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BULLETIN OF
THE NEW YORK ACADEMY
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APRIL 1939

DIAGNOSTIC SIGNIFICANCE OF CHANGES IN LEUKOCYTES*

M. M. WINTROBE

BEFORE discussing leukocytes from the diagnostic viewpoint, it will be profitable to consider some of their characters and functions. Because we are accustomed to study these cells after they have been fixed and stained, we visualize them as rounded structures with blue nuclei of various shapes, and cytoplasm of different colors and often containing granules. It is important for our understanding of them, to remind ourselves that the leukocytes are colorless corpuscles which are actively motile. The Lewises[1] have made motion pictures of leukocytes as they grow in small hanging drop cultures in autoplasma. Photographs are taken at the rate of twenty-four frames a minute, and when these are shown at the customary rate of 960 a minute the picture is a most interesting one.

The polymorphonuclear neutrophilic leukocytes are very active cells which rarely cease moving if temperature conditions are those of the body. Locomotion is ameboid in type with long pseudopods extending forward and the nucleus trailing behind. They move at the rate of 26 to 56μ per minute. The granules can be seen as tiny, round, refractile bodies completely filling the cytoplasm and streaming along in it.

* Delivered October 28, 1938 in the Eleventh Annual Graduate Fortnight

Less mature cells of this series are less active. Myelocytes are usually slow-moving in comparison with the polymorphonuclear cells and only in the metamyelocyte or juvenile stage of this series of cells does streaming of the granules, so characteristic of the mature forms, begin to appear. These granules, and the fluidity of the cytoplasm, speak for the functional activity of the cells.

The neutrophilic polymorphonuclear leukocytes are spoken of as microphages because they engulf and digest bacteria and small particles.[2] They form the second line of defense against invading organisms, after the first line, represented by the skin and mucous membranes, has been passed. They probably also play a role in the disposal of necrotic tissue and the removal of inflammatory fibrin. This is done with the aid of enzymes contained in these cells which include proteolytic enzyme,[3] amylase,[4] catalase, trypsin and oxydase.

Eosinophils are less persistently motile than neutrophils. Our conception of the function of these cells is based largely on indirect evidence and depends on the circumstances and situations in which they are found. An important role in detoxification is attributed to them, as well as in the disintegration and removal of protein, of endogenous as well as of exogenous origin.

Lymphocytes move as quickly as polymorphonuclear leukocytes and in a characteristic manner. The nucleus is at the anterior end and the cytoplasm seems to pass through "constriction rings" which appear to be static; that is, they retain their position in relation to objects external to the cell. Lymphocytes are not incessant in their movement but rest from time to time.

The lymphocyte is a mysterious cell from the functional standpoint. It is not phagocytic but seems to be involved in some way in the healing process. Lipolytic enzymes[5] have been found in these cells and have therefore been attributed a role in the metabolism[6] of fat and in the defense against antigens containing lipoids. Because of their strategic position in lymph nodes, lymphocytes have been thought to have an important role in toxin fixation. They may also be concerned in antibody formation.

Monocytes also have a characteristic type of movement. They possess a delicate surface film which is irregular or wavy in outline and the cell advances by a sort of sliding, waving motion. Monocytes contain granules and vacuoles and are actively phagocytic. Because of their liking for large particles, such as protozoa, particulate matter and red corpuscles, they are

known as macrophages and scavengers. From these cells are thought to be derived the epithelioid cell of tuberculosis, the Langhans' giant cell and the tissue macrophage or clasmatocyte (histocyte), cells which are probably important in the defense against bodies too large to be engulfed by monocytes.

The simplest method for studying leukocytes is by the examination of the wet, unstained film of blood. A drop of blood is picked up on a cover-slip. This is inverted on a slide and ringed with vaseline in order to prevent drying. The supravital technique[7] is a modification of this procedure in which certain dyes are added to the blood with the result that granules, vacuoles and mitochondria in the leukocytes are stained and the examination of the living cells is thus facilitated. The method is quite simple and does not deserve the awe in which it has been held.

For routine work, the staining of dried films of blood by one of the Romanowsky procedures, of which Wright's stain is the most popular in this country, is probably the most suitable. This method offers not only permanent preparations which may be easily transported, if necessary, but also stains the nuclei of the leukocytes, an important aid in the differentiation of the various types of cells.

Classification of Leukocytes

The use of stains for the differentiation of leukocytes is based on the brilliant investigations of Paul Ehrlich almost sixty years ago. His studies made possible the distinction of eosinophilic, basophilic and neutrophilic granules and the separation of lymphocytes and monocytes, or "transitionals" as he called them, from the myeloid series of cells.

Attempts to subdivide the leukocytes further have been confined chiefly to the myeloid series of cells. In 1904 Arneth[8] attempted to classify the circulating neutrophilic leukocytes according to the morphology of the nucleus. He subdivided these cells into five main groups, according to whether the nucleus consisted of one, two, three, four, five or more segments, and then further subdivided them as shown in Fig. 1. Such a classification was obviously too complicated and impractical. Nevertheless, the principle of his method is still used today. Arneth showed that the nucleus of the neutrophil in its development from the myelocyte of the bone marrow, becomes gradually more indented and divides, as it grows, into an increasing number of separate lobes. He also introduced the term "shift to the left" to indicate an increase in the young cells and

Fig. 1—Arneth's classification of neutrophilic leukocytes. The number of each of these cell types which he considered normal is shown in per cent.

"shift to the right" to indicate an increase in the older cells. These terms arose from the fact that Arneth recorded the number of cells of each type in a series extending from the youngest forms at the extreme left to the oldest forms at the extreme right, in the same order as shown in Fig. 1.

The first practical modification of the Arneth method was the Schilling classification (1911). Schilling divided the neutrophils into four groups, namely: (1) myelocytes; (2) juvenile neutrophils in which the nucleus is indented but not yet segmented; (3) segmented neutrophils; (4) "stabkernige" or staff forms in which the nucleus is T, V or U shaped, and unsegmented.

The stab cells are characterized by a narrow, irregular and deeply stained nucleus showing little structural detail. The characteristic differentiation of basi- and oxychromatin is absent. Such cells Schilling considers to be produced through a failure of normal maturation. He introduced the terms "regenerative shift to the left" and "degenerative shift to the left." By the former he means an increase in the proportion of young forms of neutrophils which are, however, quite normal in appearance

and are thought to be sent out from the marrow in response to an urgent demand. "Degenerative shift" refers to the presence of many stab cells and indicates the failure of young cells to mature as a result of depression of marrow function due to toxins.

In the Schilling hemogram the above mentioned types of neutrophils are classified and eosinophils, basophils, lymphocytes and monocytes are differentiated. Of these cells the juvenile neutrophils make up only 0.0 to 1 per cent and the stab cells 3 to 5 per cent.

At this point may be mentioned an anomaly of neutrophilic leukocytes which has recently attracted attention.[9] Pelger reported finding in the blood of several members of a family in Holland a great number of cells resembling juvenile or stab types of neutrophils although these persons were apparently in good health. Others have since described similar findings in members of other families and this has now come to be regarded as a rare familial anomaly of neutrophils which must be distinguished from the "shift to the left" which occurs in infections.

Innumerable other modifications of the Arneth procedure have been advocated. One of these, namely, that of Cooke and Ponder,[10] separates neutrophils into five classes according to the number of lobes. This is certainly a great simplification but it is of relatively little practical value because emphasis is placed on distinguishing polymorphonuclear leukocytes with two, three, four and five lobes. Experience has shown that such a differentiation is of relatively little importance in clinical work. Chief attention should be given to the differentiation of the younger types of neutrophils.

Other modifications of the Arneth procedure have arisen from an attempt to facilitate the differentiation of the segmented and unsegmented forms. Everyone who has tried to make a detailed differential count is aware of the difficulty of deciding whether certain cells should be placed in the unsegmented or the segmented group. The so-called filament, nonfilament count was proposed in an attempt to simplify this task. If a fine thread of chromatin can be distinguished as joining two or more lobes, the cell is classified as filamented; whereas one which shows no such thread, even though the shape of the cell nucleus is so irregular that it suggests lobulation, is classed as nonfilamented. The nonfilamented cells are said to make up 5 to 16 per cent of the leukocytes.

The chief objection to the filament, nonfilament count is that it is too arbitrary. While perhaps for some technicians a simple procedure

FIG. 2.

HARKIN'S TOXIC INDEX

$$T\ I = \frac{10\ My + 5\ J + 2\ (S - 10)}{10\ E + 2\ L + A}$$

Legend: My = myelocytes, J = juveniles, S = staff forms, E = eosinophils, L = lymphocytes, A = adult polymorphonuclears.

such as this is essential, it seems a better plan to scrutinize doubtful cells carefully and attempt to decide whether they are truly segmented or not.

It would serve no useful purpose to enumerate the various other hemograms, indexes and formulae which have been proposed for use in the study of the leukocytes. To mention some of their names will give you some idea of their nature: Walker's index of resistance, the weighted mean of Cooke and Ponder, Needle's neutrophilic graph, Boerner's nuclear index, and so on. Harkin's toxic index[11] will give you some idea of the extremes to which this desire for a formula has led (Fig. 2). These devices represent an attempt to give mathematical precision to a biologic process which does not lend itself readily to mathematics. They introduce no new morphologic criteria but, instead, enshroud a relatively simple subject with an air of complexity and mysticism.

A discussion of the neutrophilic leukocytes would be incomplete if attention were not called to the significance of qualitative changes in the cytoplasm of neutrophils.[12,13] In the presence of severe infections, some of the granules of the neutrophils which normally are small, uniform in size, pink in color, and regularly dispersed, stain more deeply. These basophilic granules, as they are called, may be small and distributed among the normal pinkish granules, or they may be quite large, few in number, and no normal granules may be seen. Abnormality of the cytoplasmic structures of the neutrophils is also indicated in such cases by the appearance of the cells after staining by the peroxidase method. Normally, neutrophilic cells are full of oxidase staining granules. When basophilic granulation is demonstrable by one of the Romanowsky staining methods, few oxidase reacting granules are found in the cells.

The toxic granules may be present in either young, immature cells or in the mature, segmented forms. In addition to these changes, evidence

of cell damage may be found in neutrophils in the form of bluish staining or vacuolization of the cytoplasm. In rare instances one may see neutrophils entirely lacking in specific granules.[14]

It is, of course, of extreme importance to prepare and stain blood slides carefully when the morphologic differences above mentioned are sought. For differential blood counts, thin films of blood on cover glasses give much better preparations than smears made on slides. It is important to avoid over-staining and it is wise to make control preparations of normal blood, stained in the same way as the preparations of the patient's blood. Before assuming that a given preparation shows "toxic" granules and "stabkernige," one must be sure that similar changes are not observed in normal blood, similarly stained. If the blood film is made on a slide, it is a good plan to make a film of normal blood at one end of the slide and a film from the patient's blood at the other. The whole slide can then be stained at the same time.

It was stated above that in the differential examination of the neutrophils, emphasis should be placed on the younger forms rather than on the multi-segmented types. There is one type of cell to which reference should be made, however. This is a polymorphonuclear leukocyte which is unusually large and which possesses a nucleus of six to ten lobes. This type of cell is sometimes called a macropolycyte and is characteristically seen in the blood of cases of pernicious anemia. It is rarely seen in other conditions.

It has not been shown conclusively that a maturation cycle can be distinguished among the lymphocytes of the blood such as occurs in the myeloid series. Lymphocytes have been classified as large and small, usually on the assumption that the former are the less mature cells. However, there is no adequate evidence that the size of lymphocytes is a criterion of their age.[15] Wiseman[16] has recently recommended the differentiation of lymphocytes as young, mature and old on the basis of differences in the degree of basophilia of their cytoplasm, number of mitochondria, and degree of pyknosis of the nucleus and has reported significant alterations in the Y : M : O ratio in tuberculous infection particularly. In practice, Wiseman's differentiation of the lymphocytes is difficult even if it is admitted that it is theoretically sound—something which not all hematologists are ready to do.

In summary, then, a simple and practical classification of the leukocytes normally occurring in the blood is one which distinguishes the three

TABLE I

RELATIVE AND ABSOLUTE VALUES FOR LEUKOCYTE COUNTS IN NORMAL ADULTS PER C.MM. BLOOD

Type of Cell	*Per cent*	*Absolute Number*		
		Average	*Minimum*	*Maximum*
Total leukocytes		7,000	5,000	10,000
Myelocytes	0	0	0	0
Juvenile neutrophils	3-5	300	150	400
Segmented neutrophils	54-62	4,000	3,000	5,800
Eosinophils	1-3	200	50	250
Basophils	0. -0.75	25	15	50
Lymphocytes	25-33	2,100	1,500	3,000
Monocytes	3-7	375	285	500

classes of leukocytes, namely, lymphocytes, monocytes and granulocytes, and subdivides the latter not only according to the type of granulation but according to the age of the cells, namely, juvenile forms and segmented forms (Table 1). In addition, attention should be given to so-called "toxic" changes in the nuclei and cytoplasm of these cells.

Further consideration cannot be given here to the subject of the morphological characteristics of the leukocytes. It may be stressed, however, that in learning to differentiate these cells one should acquire the habit of systematically examining the whole cell. One should note the size and shape of the nucleus, the nature of the chromatin, the presence or absence of a nuclear membrane, a perinuclear clear zone, and nucleoli, as well as the color of the cytoplasm, the size, color and number of granules within it and the presence of any unusual structures. By so doing, one will acquire the habit of seeing all one looks at and in time cells will be distinguished quickly because of an automatic recognition of these differences. The actual identification of cells regarding which there is some doubt can be made only by weighing the evidence for and against each type of cell considered.

TECHNICAL ERROR AND PHYSIOLOGIC VARIATIONS

Before discussing the changes which occur in leukocytes in disease, we must consider the variations which may be attributed to technical error as well as the fluctuations which occur under physiologic conditions.

By the term "technical error" we refer to the errors unavoidably associated with the methods employed rather than those attributable to the defective technique of the examiner. The latter, of course, may be very great and has sometimes led to grave errors in diagnosis.

It is generally agreed by those who have investigated the subject, that the apparatus of responsible manufacturers in the hands of experienced workers, introduces almost negligible variations as the result of filling the sampling pipet, dilution of the sample, variations in the calibration of the appliances, and the personal factor of counting. The chief error occurs in the mixing of the cells and diluting fluid, filling the counting chamber by capillarity and settling of cells by chance on the ruled field of the counting chamber.[17] The mean error due to these causes amounts to possibly as much as 600 cells when the leukocyte count is normal (7000) and an area of only 4 square millimeters (one chamber) is counted, or about 425 cells if the count is made in two chambers ($e = \sqrt{N}$, when e is the mean error and N is the number of cells counted[18]). When the leukocyte count is, say 16,000, the probable error would be about 900 if the count were made in one chamber only. Thus for these two levels of leukocyte count one should consider ranges of 6400 to 7600, and 15,100 to 16,900, respectively, as within the range of error of distribution.

Another question of great importance in the interpretation of the leukocyte count, is the significance of a change in the percentage of cells, let us say from 70 per cent polymorphonuclears to 80 per cent. Again assuming that the differential count has been done carefully on well stained preparations, two factors must be considered. One is the manner of preparation of the blood film, whether on cover-slips or on slides. It is generally agreed that in smears drawn or pulled on slides, the larger leukocytes tend to accumulate at the margins while the smaller cells are distributed in the central portion of the film. If it is not possible to make cover-slip preparations, a zig-zag course about the edge of the slide-smear should be followed.

The second source of error is one of chance distribution. This error is reduced as the number of cells examined is increased. Statistical studies show that a minimum of 200 cells should be counted.[18] The error is considerably less when this number of cells is counted than when only 100 cells are enumerated. Goldner and Mann[19] have published "confidence curves" from which one may estimate the probable error of a differential count when 200 cells are counted. According to these curves

one may, 19 times out of 20, expect the true proportion of polymorphonuclears to be somewhere between 63.6 and 76.4 per cent when the count is found to be 70 per cent. Accordingly, a count of 80 per cent on the same patient at another time could probably be considered as being significantly increased. However, if the count were made on only 100 leukocytes, the difference would be scarcely significant.

I should like to lay some emphasis on the subject of error in leukocyte counting, because in general physicians are not sufficiently critical of this, as of many other laboratory procedures. Because the results are expressed numerically, many derive a false sense of accuracy from them. It is important to scrutinize the figures as carefully as one examines the patient. In fact, it is probably even more important to do so because the physician usually examines the patient himself whereas the laboratory studies are often left to an assistant.

Another matter of some importance is the physiologic variation of the leukocyte count.[20] It is generally stated that the normal range of the leukocyte count is 5000 to 10,000. It is not sufficiently recognized that in 11 per cent of apparently normal persons values above 10,000 are found.[21] Then again, in some persons the leukocyte count is normally well below 10,000 and this figure in them represents a pathological leukocytosis. Furthermore, the state of physical and mental rest influences the leukocyte count and fluctuations normally occur during a single day as well as from day to day. Under conditions of complete mental and physical rest a basal level of 5000 to 7000 cells is usually attained. The random activity of ordinary routine is often associated with a moderate increase and higher levels are found in the afternoon than in the morning. Digestion of food probably does not cause appreciable leukocytosis as was formerly the opinion.

Strenuous exercise or convulsive seizures cause a well marked leukocytosis, even as high as 35,000. It is important for the physician to bear in mind, moreover, that fear and apprehension, pain and even nausea and vomiting may produce leukocytosis. The injection of adrenalin and ether anesthesia do the same. It is important to note, however, that the leukocytosis produced by these factors is not characterized by an increase in young cells in the blood. Consequently a differential leukocyte count is of great importance in distinguishing physiologic from pathologic leukocytosis.

TABLE II

FACTORS INFLUENCING THE MAGNITUDE OF NEUTROPHILIA

1. The cause of the neutrophilia; pyogenic, especially coccal vs. typhoid or tubercle bacilli
2. Localization of the process; then even tubercle bacilli may cause neutrophilia
3. Virulence of the organism, reactivity of the patient

Numerical increase = resistance of the individual
Percentage increase } = effort of the response
Toxic Changes }

TABLE III

CAUSES OF NEUTROPHILIA

1. Acute infections, especially coccal
   Certain bacteria, fungi, spirochetes, viruses and parasites
   Localized infections
   Certain general infections, such as rheumatic fever, diphtheria, smallpox
   Development of complications in diseases usually not associated with neutrophilia
2. Intoxications
   (A) Metabolic; uremia, diabetic acidosis, eclampsia, gout
   (B) Poisoning by chemicals and drugs; lead, mercury, digitalis, adrenalin
   Insect venoms; black widow spider
   Foreign proteins, after a preliminary leukopenia
3. Acute hemorrhage
4. Postoperative
5. Non-inflammatory conditions, such as coronary thrombosis
6. Malignant neoplasms when growing rapidly, especially in G-I tract, liver, bone marrow
7. Sudden hemolysis of red corpuscles
8. Physiological in the newborn, during labor, after strenuous exercise, after repeated vomiting, convulsions, paroxysmal tachycardia
9. Myeloid leukemia and erythremia

TABLE IV

CAUSES OF LEUKOPENIA

1. Certain infections
   (A) Bacterial; e.g., typhoid, paratyphoid, undulant fever
   (B) Infections caused by viruses; e.g., influenza, measles, rubella
   (C) Protozoal infections; e.g., malaria, relapsing fever, kala-azar
2. All types of overwhelming infections; e.g., miliary tuberculosis, septicemia; and cachectic and debilitated states and inanition
3. Certain conditions of unknown causation; e.g., catarrhal jaundice, cirrhosis of the liver, Felty's syndrome, lupus erythematodes disseminatus
4. Hemopoietic disorders, especially those involving the spleen; Banti's disease, Gaucher's disease; also in pernicious anemia (relapse), chronic hypochromic anemia, aplastic anemia, myelophthisic anemia, idiopathic granulocytopenia
5. As the effect of recognized toxic agents
   Chemical; e.g., benzol, arsenic, lead, bismuth, mercury, antimony, amidopyrine
   Physical; e.g., radioactive substances
6. In anaphylactoid shock and in early stages of reaction to foreign protein

Variations of Leukocytes in Disease

It is unnecessary to enumerate in detail all of the conditions in which various types of leukocytic reaction occur. However, some of the general principles which underly these changes may be considered with advantage.

Leukocytosis is usually due to an increase in the number of cells of the neutrophilic series. We shall refer to this type of leukocytosis as neutrophilia for the sake of clarity.

Three factors influence the magnitude of neutrophilia (Table II). These are: (1) the cause; (2) the localization of the process; and (3) the virulence of the invading organism, the reaction of the patient and his general resistance. In general, pyogenic and particularly coccal bacteria call forth a neutrophilic response, whereas other bacteria such as typhoid and the tubercle bacillus have no such effect. However, a generalized infection, even when it is the result of the invasion of cocci, is often not associated with an increase in the total leukocyte count. So important is the factor of localization that if the infection is delimited, neutrophilia may result even when the invading organism is one which usually is associated with leukopenia. Tuberculous meningitis is an example of this. Finally, with reference to the third factor, it is generally appreciated that when an infection is mild, neutrophilia may be absent and when it is overwhelming and the person involved too feeble to resist, neutrophilia may not occur. In general, the total numerical increase in neutrophils may be regarded as indicating the resistance of the individual to an infection while the percentage increase of these cells and the qualitative changes indicate the effort of the response and the severity of the infection. Thus in the presence of an overwhelming infection, the total leukocyte count may not be increased, but there is a marked "shift to the left," the nuclei of many of the juvenile neutrophils are pyknotic and toxic granulation is found in their cytoplasm.

The causes of neutrophilia have been summarized in Table III. The causes of leukopenia are listed in Table IV.

At this point reference may be made to what is known as the "leukopenic index." This refers to leukopenia which is said to occur in allergic individuals following the ingestion of food to which they are sensitive. When carried out under certain conditions as described for the test, a decrease in the leukocyte count of 1000 or more cells per c.mm. is inter-

TABLE V

CAUSES OF EOSINOPHILIA

1. Allergic disorders; bronchial asthma, urticaria, angioneurotic edema, hay fever
2. Skin diseases; especially pemphigus and dermatitis herpetiformis
3. Parasitic infestations; especially parasites which invade the tissues; e.g., trichinosis, echinococcus disease, less regularly in intestinal parasitism
4. Certain infections; e.g., scarlet fever, chorea, erythema multiforme
5. Certain diseases of the hemopoietic system; chronic myeloid leukemia, erythremia, Hodgkin's disease, after splenectomy, pernicious anemia
6. Miscellaneous disorders; periarteritis nodosa, tumors of the ovary or those involving serous surfaces or bones; certain types of lung infiltration
7. As a familial abnormality

TABLE VI

SEE PG. 768 FOR CORRECTION

CAUSES OF LYMPHOCYTOSIS

1. Certain acute infections; pertussis
   infectious mononucleosis
2. During subsidence of acute infection and recovery phase of granulocytopenia
3. Many protozoal infections: malaria, Rocky mountain spotted fever, kala-azar, trypalant fever
4. During the stage of convalescence from an acute infection
5. Exophthalmic goitre (usually only relative lymphocytosis)
6. Infants and young children, especially in the presence of rickets and malnutrition
7. Lymphatic leukemia

TABLE VII

CAUSES OF MONOCYTOSIS

1. Certain bacterial infections: tuberculosis, subacute bacterial endocarditis, brucellosis, typhus, rarely in typhoid
2. During subsidence of acute infection and recovery phase of granulocytopenia
3. Many protozoal infections: malaria, Rocky mountain spotted fever, kala-azar, trypanosomiasis, oriental sore
4. Hodgkin's disease; also in diseases of disturbed lipoid metabolism, such as Gaucher's disease
5. Monocytic leukemia
6. Tetrachlorethane poisoning

preted as indicating incompatibility of food. This method has also been proposed as a means of detecting other forms of allergy. In the light of what has already been said regarding the unavoidable error in leukocyte counting, it is no wonder that this test has been the subject of considerable criticism.[22] Nevertheless, it has its ardent advocates.

The causes of eosinophilia are listed in Table V. It is noteworthy that whereas eosinophilia occurs as a characteristic of a small number of infections,[23] in general eosinophils disappear when neutrophilia occurs. This phenomenon has been called "Simon's septic factor." Recovery in such cases is often marked by eosinophilia.

The basophilic leukocytes are found increased in chronic myeloid leukemia and in erythremia, and sometimes in chronic hemolytic anemia, in chlorosis, following splenectomy, in Hodgkin's disease, in smallpox and in chickenpox and following the injection of a foreign protein, as well as in chronic inflammation of the accessory sinuses.

The causes of lymphocytosis are enumerated in Table VI. This refers to absolute lymphocytosis. Relative lymphocytosis occurs in most of the conditions associated with neutropenia.

Plasma cells are rarely found in the circulating blood. They have been noted in rubella, in scarlatina and in measles.[24]

The causes of monocytosis are listed in Table VII. The role of the monocyte in tuberculosis has attracted intensive study and it has been shown that this cell takes an important part in the cellular reaction to the tubercle bacillus. The lipoids of this organism are phagocytized by monocytes, are partially degraded within them and cause their transformation to epithelioid cells. This activity is reflected in the circulating blood and it is now generally accepted that monocytosis in a tuberculous patient is an unfavorable sign. Increasing reliance is being placed on the ratio of monocytes to lymphocytes, for the latter vary inversely with the former in this disease, and lymphocytosis occurs when the tuberculous lesion is healing. Normally there is one monocyte to at least three lymphocytes. In tuberculous infections, a favorable M : L ratio is 1 : 3.6, while a ratio of 1 : 0.8 is a very unfavorable one. At the same time the proportion of young lymphocytes decreases, a phenomenon which Wiseman[25] has named "curve of degeneration." Improvement in tuberculosis, he has found, is associated not only with a fall in the number of monocytes, but an increase in the number of young lymphocytes ("curve of regeneration"), and in the total number of lymphocytes. These

changes in the leukocytic picture may appear some time prior to other indications of the change in the status of the patient, and thus are of great prognostic value.

Prognostic Value of the Leukocytic Picture

Study of the leukocytes is clearly of value as an aid in diagnosis. A painstaking differential count may be particularly helpful in discovering cryptic infections of subacute or chronic types in which there is no increase in the total leukocyte count. When several counts have been made, the leukocyte picture may be a useful aid in estimating prognosis. In Table VIII various factors which are of importance in the estimation of prognosis on the basis of the leukocyte count are listed. All of these have already been referred to and only certain principles need now be mentioned.

Generally, three phases may be observed in the leukocytic reaction to an infection.[26] During the progressive stage, neutrophilia predominates and the severity of the infection as well as the reaction of the patient may be gaged by the magnitude of the leukocyte count, the degree of "shift to the left" and the presence of toxic cytoplasmic granulation. Thus, a slight neutrophilia with slight nuclear "shift" suggests a mild infection, whereas a moderate leukocytosis with moderate "shift" (say, 16 per cent of young forms), together with disappearance of eosinophils and decrease of lymphocytes, signifies a moderately severe infection. As already stated, still more marked leukocytosis or a fall in the leukocyte count, with an even greater "shift to the left" than before, are grave signals. Unfavorable signs in the leukocyte picture are listed in Table IX.

Except in certain diseases, such as tuberculosis, in which an increase in the number of monocytes is an unfavorable sign, the reappearance of these cells in the course of an acute infection usually indicates the beginning of the recovery stage. Their return is often followed by the reappearance of eosinophils. Finally, lymphocytosis develops during the period of convalescence. The changes in the blood picture during recovery are shown in Table X.

By a consideration of the details of the leukocyte count, then, and particularly by noting the changes which occur from day to day, a valuable estimate of the course of the patient's illness can be made, sometimes before other signs are manifest.

TABLE VIII

ESTIMATION OF PROGNOSIS FROM LEUKOCYTIC COUNT
SIGNIFICANT FACTORS

1. Magnitude of leukocyte count
2. Proportion of immature cells
3. Number of "toxic" forms of leukocytes
4. Degree of reduction in number of eosinophils
5. Degree of reduction in number of lymphocytes
6. Degree of increase in monocytes (tuberculosis)

TABLE IX

UNFAVORABLE SIGNS IN THE LEUKOCYTIC PICTURE

1. Extremely high total number of leukocytes with high percentage of neutrophils; or
2. Failure to develop leukocytosis
3. High proportion of immature cells especially if they outnumber mature forms
4. Absence of eosinophils
5. Marked absolute reduction of lymphocytes
6. Presence of numerous toxic, degenerative forms

TABLE X

CHANGES IN BLOOD PICTURE DURING RECOVERY

1. Falling total leukocyte count with diminishing proportion of neutrophils
2. Decrease of immature forms
3. Temporary increase of monocytes
4. Reappearance or increase of eosinophils
5. Increase in number of lymphocytes
6. Absence or decrease of toxic forms

TABLE XI

LEUKEMOID BLOOD PICTURE

1. Infections; presenting pictures resembling
   myeloid leukemia; pneumonia, meningococcus meningitis, diphtheria, tuberculosis, lymphoid leukemia, whooping cough, chickenpox, infectious mononucleosis
2. Intoxications; eclampsia, severe burns, mercury poisoning
3. Malignancy; especially with bone metastases; also multiple myeloma, myelofibrosis, Hodgkin's disease
4. Severe hemorrhages; sudden hemolysis of blood

Leukemoid Blood Picture

In rare instances the leukocytic response to disease may be so marked or of such a character that the blood picture resembles that seen in one of the types of leukemia. These have been termed leukemoid blood pictures and a number of such reports are found in the literature. In some instances it has only been the magnitude of the leukocytic reaction or its unusual quality which suggested leukemia. In many cases, however, severe anemia accompanied the leukocytic change and even nucleated red corpuscles of various types were found. In some instances even the clinical picture, because of fever, hemorrhages, splenomegaly or adenopathy, suggested leukemia. The true diagnosis of some of these cases was evident only on postmortem examination.

In Table XI, conditions in which leukemoid pictures have been observed are listed. In the infections, extremely high leukocyte counts have sometimes been found, even as high as 112,000 in cases of septicemia,[27] 176,000 in whooping cough,[28] 81,200 in chickenpox[29] and 63,000 in infectious mononucleosis. It is in association with tuberculosis, however, that leukemoid pictures have been most frequently described.[30,31] The tuberculosis has usually been miliary in type or it involved the lymph nodes or spleen. The leukocytic picture in such cases has resembled most often that of acute myeloblastic leukemia and leukocyte counts as high as 156,000 have been reported.

In a case of eclampsia a leukocyte count of 100,000 has been recorded, while in an instance of mercury ointment poisoning, 69,500 leukocytes with 24 per cent myelocytes, were found.[32] In a case of Hodgkin's disease, a leukocyte count of 250,000 has been reported.[33]

These examples of leukemoid pictures are, of course, extremely rare. They are mentioned here only to emphasize the importance of taking into consideration the whole clinical picture rather than a single finding in making the diagnosis.

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PRELIMINARY REPORT OF THE USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA*

NORMAN PLUMMER AND HERBERT ENSWORTH

Less than a year has passed since the first reports appeared in the English literature, describing the experimental studies on sulfapyridine (M & B 693). The clinical experience with this drug is still very much limited. Nevertheless, most of us working in pneumonia investigation are already willing to concede that this new drug definitely influences the course of the pneumococcus infection and quite probably increases the chances of recovery. The mode of action remains remarkably obscure, and it is too early to be completely assured that serious reactions do not occur.

Sulfapyridine has been used on the medical services of New York Hospital and the First and Second Divisions of Bellevue Hospital during the past three months and it is our privilege to report this experience. During this period, the drug has been administered to 111 patients, of whom eighty-eight were diagnosed pneumonia. The drug was given by mouth in all cases. The initial dose was usually 2.0 grams; subsequent doses of 1.0 gram were given every four hours until the desired therapeutic effect had been obtained. Most of the patients in the total series received an average of 16.0 grams. In some the preparation was discontinued after a few grams had been given because of the severe nausea and vomiting produced. In a few cases a much larger total dosage was administered; in one instance 46.0 grams. All of the patients except two were hospitalized, consequently their progress was closely followed by the routine blood counts, urine analyses, and other indicated tests. All of the pneumonias had at least one sputum typing, one blood culture, and all except a very few had one or more chest x-ray examination. A few of the more recent cases have had blood sulfapyridine determinations.

From the start of this investigation of sulfapyridine, particular atten-

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This investigation has been conducted under a grant of the Josiah Macy Jr. Foundation.

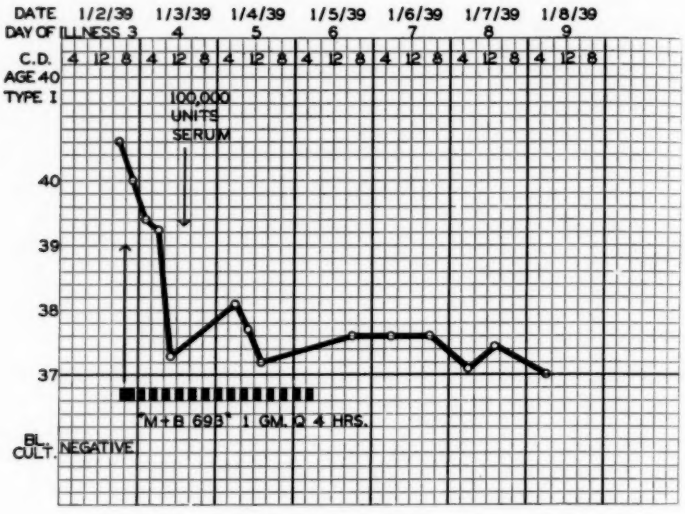

Chart 1—This is the chart of a forty year old woman admitted to Bellevue on the fourth day of illness. Sulfapyridine, 2 grams, was given by mouth shortly after admission. The drug was continued at four hour intervals in 1 gram amounts during the next two days. The temperature dropped to nearly normal on the following day after 5 grams of sulfapyridine had been given. The blood culture taken on admission was negative. The sputum typing was not complete until the day after admission when it was reported Type I. Even though the temperature was normal it was thought wise to give 100,000 units of Type I antipneumococcus serum.

tion has been focussed upon the occurrence of untoward effects. In the total series of 111 cases, during the three-month period of this study, we have encountered no serious reaction to the drug in the dosage given. The blood counts have revealed no particular changes in the red or white cells. The urine analyses showed only the occasional trace of albumin which occurs in febrile conditions. A few patients had a mild icterus such as is occasionally seen during the course of pneumonia. In this series, there was no case of toxic hepatitis, neuritis, nephritis, or agranulocytosis, —complications known to occur in pneumonia, but which must be ruled out as possibly being related to the therapeutic agent used.

The principal disadvantage of sulfapyridine is its effect on the gastro-intestinal tract. Nausea and vomiting frequently occur; 55 per cent of the patients had nausea and 40 per cent had both nausea and vomiting.

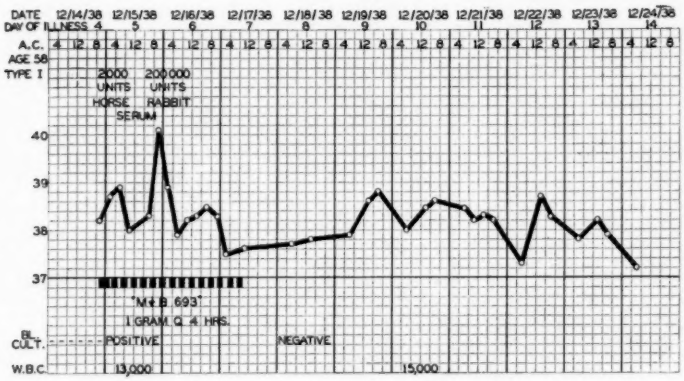

Chart 2—A fifty-eight year old patient with Type I pneumonia and a positive blood culture, treated with sulfapyridine and serum. This therapy controlled the toxemia and septicemia. On the day after admission to the hospital, there were physical and x-ray signs of fluid, which on thoracentesis was found to be a thin exudate, culturing Type I pneumococci. The fluid was quickly absorbed and surgery has not been necessary, although the convalescence has been considerably retarded.

In about 10 per cent of the cases it was necessary to discontinue the therapy because of the severity of these symptoms. The question has arisen whether the gastric irritability is of local or central origin. The fact that the chemical when chewed in the mouth is so bland and innocuous, together with the finding that nausea usually does not occur until after four to six grams have been given, seems evidence in favor of the central origin. Blood determinations should aid in answering this problem.

We come now to the important question: What is the value of sulfapyridine in the treatment of pneumonia? The series which we have for analysis includes eighty-eight patients having definite signs of pneumonia, in whom chronic pulmonary disease has been excluded by the course and bacteriological findings. We have included both the typical and atypical acute pneumonias; also cases in which the pneumonia occurred as a complication of serious systemic disease. Patients who died shortly after admission to the hospital have also been included. We have carefully excluded cases of influenza and acute bronchitis. Twenty of the eighty-eight patients received specific antipneumococcus serum in addition to sulfapyridine.

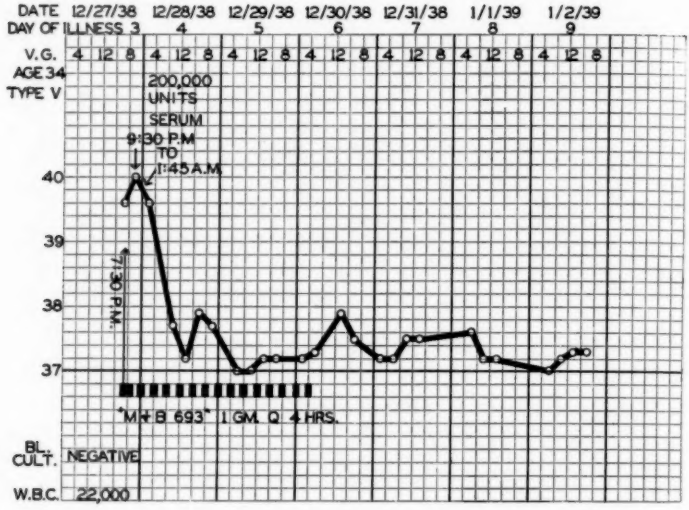

Chart 3—A thirty-four year old man admitted on the third day. On admission, the sputum showed Type V pneumococci, the blood culture was negative, and the white blood cell count was 22,000. Both sulfapyridine and serum were given with a quick and positive response.

The mortality rate in this series of eighty-eight cases is 8 per cent,** seven of the patients having died. This is an extremely low figure when compared with an expected fatality rate of from 25 per cent to 35 per cent in similar groups of cases. However, a number of factors must be taken into consideration in estimating the accuracy of this figure. The series is small; the mortality rate in pneumonia is usually lower in the fall and early winter season than in the late winter; there are indications that pneumonia recently has been of a milder form. Also, the series contains more than the average number of pneumonias caused by the higher types and the unclassified pneumococcus, forty-one of the eighty-eight cases falling in this group. The percentage of septic cases is only 6 per cent, which is low. On the other hand, the incidence of systemic disease is high. Also, in the series of eighty-eight patients, nineteen were

** The total series at the time of publication included 157 cases of pneumonia with fifteen deaths, a mortality rate of 9.5 per cent. Thirty-six patients had Type III pneumonia, of which two died, a mortality of 5.6 per cent. Forty-eight of the patients were given both serum and sulfapyridine and of this group, two died, a mortality of 4.1 per cent.

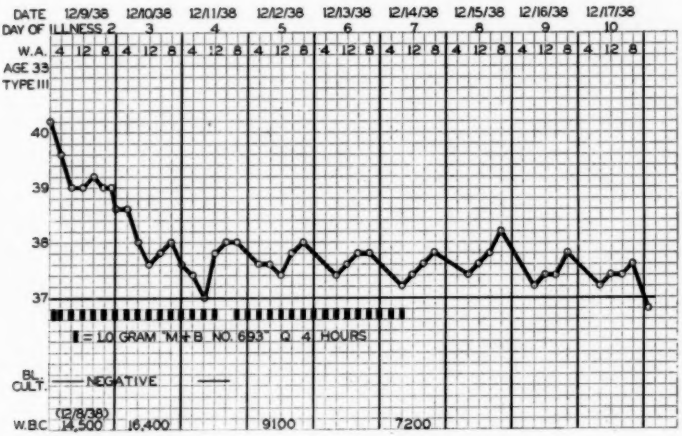

Chart 4—A thirty-three year old woman admitted to New York Hospital, the day following an acute onset. On admission, the sputum showed Type III organisms, the blood culture was negative, and the leukocytes were 14,500. Sulfapyridine was started promptly, and because of extensive pulmonary involvement was continued until 32 grams had been administered. Although the temperature did not drop to normal until the tenth day, the severe toxemia was quickly controlled. The leukocyte count rose from 14,500 to 16,400 after the sulfapyridine was started, and even though 32 grams of the chemical were administered, there was no evidence of agranulocytosis during the hospital stay. This patient had practically no gastrointestinal disturbance from the drug.

over fifty-five years of age, and twenty-four had Type III infection.

The mortality rate in the Type III pneumonia is only 8 per cent, two of the twenty-four cases having died. Three of the Type III cases had positive blood cultures, and two of these recovered. Again there are too few cases from which to make any deductions.

A brief description of the seven fatal cases is important for a fair analysis of our results. Two of the deaths were from Type III infection, one of whom died twelve hours after admission to Bellevue, the blood culture plate showing innumerable Type III colonies, and the patient having received only 6 grams of sulfapyridine. The other Type III fatality was a bad alcoholic, in whom the diagnosis of pneumonia was not made until a few hours before death and to whom only 3 grams of the drug had been administered. The only other patient with a fixed type

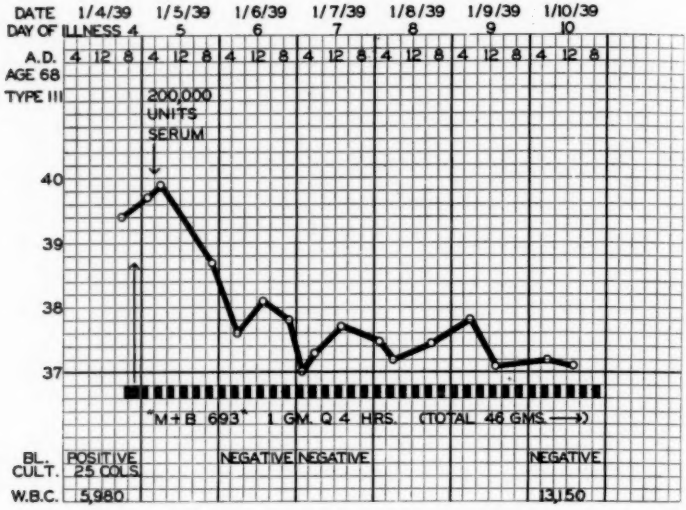

Chart 5—This case alone gives evidence that we now have available, therapeutic agents more effective than any previously used. This sixty-eight year old woman was admitted to Bellevue on the 4th day of a very acute illness. On admission the sputum showed Type III pneumococci and the blood contained 25 Type III organisms per cubic centimeter. The leukocyte count was only 5,980. Sulfapyridine was started as soon as the clinical diagnosis of pneumonia was made. Early on the second day 200,000 units of rabbit serum were injected intravenously. The toxemia and septicemia were quickly controlled. The white blood cell count rose from 5,980 to 13,150 during the period that sulfapyridine was given. Because of the grave prognosis in such a case, the drug was continued until 46 grams had been given. There was no gastric irritation, and no other untoward reaction.

who died, showed a Type IV in the sputum. In this case there was definite response to 17 grams of sulfapyridine, but a few days later, the patient died suddenly after a huge, foul lung abscess had commenced draining. Two patients regarded as having unclassified pneumococcus pneumonia died. One of these was seventy-eight years of age. The other had had pulmonary symptoms for six weeks or more, had been in Bellevue for two weeks and was treated with sulfapyridine just a few days before his death. In both of these cases there is some question as to the true bacteriological diagnosis. The remaining two fatalities occurred in the New York Hospital series. One was a man of sixty-three years, with

arteriosclerotic heart disease and auricular fibrillation who developed an acute pneumonia and was given in all 10.0 grams of sulfapyridine. There seemed to be satisfactory response to the drug, but two days after it had been discontinued, he suddenly developed severe pain in the chest and died. The other was one of pulmonary infarct and pneumonia following pregnancy. The foul, purulent sputum which the patient had, showed Friedländer's bacilli along with other aerobic and anaerobic organisms. Again the patient showed a temporary response to sulfapyridine, but died later with empyema and other complications. It is evident that the mortality rate would be reduced even further if some of the questionable fatal cases were excluded from the series. The possibility of a relationship between the deaths and the use of sulfapyridine in the patients with coronary disease and lung abscess has been considered but seems remote.

The clinical response to sulfapyridine is as convincing as the reduction in mortality rate. With remarkable regularity the temperature drops to normal within from twenty-four to thirty-six hours after the therapy is instituted. Such a response occurred in forty-five of the eighty-eight cases, and in a number of others the response was a very satisfactory one. The active phase of the disease is considerably shortened, although the signs of consolidation seem to run through their usual cycle. A mild cyanosis occurred in a small percentage of the cases. In no case did the white blood cells drop to a low figure. There were, however, several cases with initial leukopenia, in which the white blood cells returned to a more normal figure following the drug.

Serum therapy (in most cases rabbit serum) was given to twenty of our eighty-eight patients. The results in this group are particularly striking. All of the patients recovered. There was a spectacular drop in temperature in every case. The series included three patients with positive blood cultures, one of whom was a Type III with twenty-five organisms per cubic centimeter on the initial blood culture examination. On the other hand, the serum-treated group included only cases of typical pneumonia. Furthermore, in some of these, as will be demonstrated in the charts, the serum was administered after the temperature was normal.

In summarizing, it should be emphasized again, that this is a preliminary report, and that on such a limited experience no positive conclusions can be drawn. In our results there is some evidence that a combination of sulfapyridine with serum gives greater benefit than either the serum or the chemical alone. But until we can ascertain the relative values

of serum alone, sulfapyridine alone, or a combination of both—our present method of type diagnosis and serum treatment should not be changed. For ourselves and the several people working with us, this recent experience has been most encouraging, and seems to point the way to a more effective treatment of pneumonia.

PRELIMINARY REPORT OF THE USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA*

HARRISON FITZGERALD FLIPPIN

IT IS indeed a great pleasure for me to be here tonight and hear these brilliant presentations on the treatment of pneumonia in New York City. Our group in Philadelphia, which is composed of Dr. John S. Lockwood, Dr. D. Sergeant Pepper, Dr. Leon Swartz, and myself, first became interested in the treatment of pneumonia with sulfapyridine last August. Our interest in this chemotherapeutic agent was stimulated by the investigative work of one of us, Dr. John S. Lockwood, on the action of sulfanilamide, which has gained considerable recognition; and secondly, our interest was stimulated by the work of Gaisford and Evans in England, who have reported 200 cases of pneumonia treated alternately with sulfapyridine. Of the 100 cases treated with sulfapyridine the mortality rate was 8 per cent as compared with 27 per cent in the control series, which received other forms of therapy. Naturally, when a new therapeutic agent, especially a chemotherapeutic agent, is presented for the treatment of pneumonia, and particularly in the city of Philadelphia, it meets with a great deal of opposition. I am happy to say, however, that sulfapyridine has been enthusiastically received by a number of the Philadelphia physicians.

Tonight I would like to present the first 100 cases (Table I) of pneumonia which we have treated in Philadelphia with sulfapyridine since last August. Of this group we were able to detect the pneumococcus either from the sputum or blood stream in eighty-three of the cases; in the remaining seventeen cases we were not able to detect the specific pneumococcic organism from the sputum or blood stream, although in several instances we were able to find the group to which they belonged. As noted on the table, we have not included three fatal cases which received treatment for less than twelve hours. These represented terminal

* Presented January 17, 1939 before the Section of Medicine.

TABLE I

Type	*Number*	*Deaths*	*Type*	*Number*	*Deaths*
I	21	0	XIV	5	0
II	7	0	XV	2	0
III	14	3	XVII	1	0
IV	5	1	XIX	2	0
V	5	0	XXIII	1	0
VI	4	0	XXVII	3	0
VII	6	0	XXIX	1	0
VIII	6	0	Others	17	1
	68	4		32	1

TOTAL

Cases..... 100 Deaths..... 5

(3 fatal cases treated for less than 12 hours not included)

TABLE II

Toxic Reactions	*Number*
Nausea	42
Vomiting	
Troublesome	24
Severe	9
Dermatitis	1
Acute Hemolytic Anemia	1
Leukopenia	1
Drug Fever	1

cases of pneumonia which received no more than two doses of the drug and for that reason I did not think that we should include them in the above report.

Naturally, when a new drug is being considered, the first question that comes into the mind of the physician is, what are the toxic effects of this preparation? As far as the toxic reactions, as can be seen by Table II, the gastrointestinal symptoms are the most important. In any acute infection, as pneumonia, we expect a certain amount of gastrointestinal irritability, and it is not surprising that the oral administration of the drug should result in some untoward reactions. The problem of vomiting is the most important toxic reaction which confronts us at this time. As we all know there is a definite chloride deficiency during pneumonia, and with this added vomiting we get a marked loss of chlorides. With this in view we have given rather large dosages of salt solution intravenously, and believe that this procedure has diminished the severe vomiting. In

a number of instances the discontinuance of the drug for one or two doses has brought cessation of the vomiting. We have also introduced the drug through a nasal catheter into the duodenum with beneficial results. Rectal administration has proved unsuccessful. As noted on Table II, we have made no reference to cyanosis as a toxic reaction. We have seen rather severe cyanosis in about 10 per cent of our cases, but it is difficult to determine whether the cyanosis is due to the drug or is associated with the pneumonia. In closing, I wish to say again that we are quite enthusiastic thus far regarding the efficacy of sulfapyridine in the treatment of pneumococcal infections.

PRELIMINARY REPORT OF THE USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA*

The Absorption, Acetylation and Excretion of Sulfapyridine

H. E. STOKINGER

I WILL attempt to review briefly some preliminary analytical results on the fate of sulfapyridine (M & B 693) in laboratory animals and patients at the Presbyterian Hospital, Columbia Medical Center.

It should be said at the outset that M & B 693 bears certain analogies to sulfanilamide: 1) the detoxification process is one of acetylation, 2) it may be estimated quantitatively in body fluids by methods that involve no new procedure. This latter allows the drug to

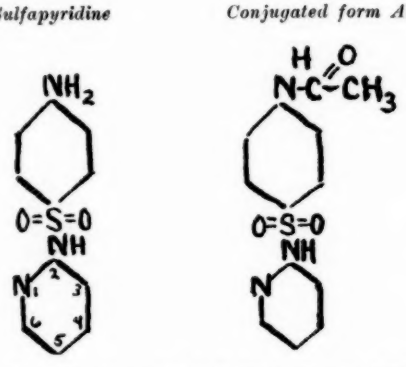

Fig. 1—Detoxification of M & B 693 in Man and Rabbits

be followed in a fairly convenient manner during its course through the body.

The formula on the left represents the chemical constitution of the M & B 693, officially named recently Sulfapyridine by the American

* Presented before the Section of Medicine, January 17, 1939.

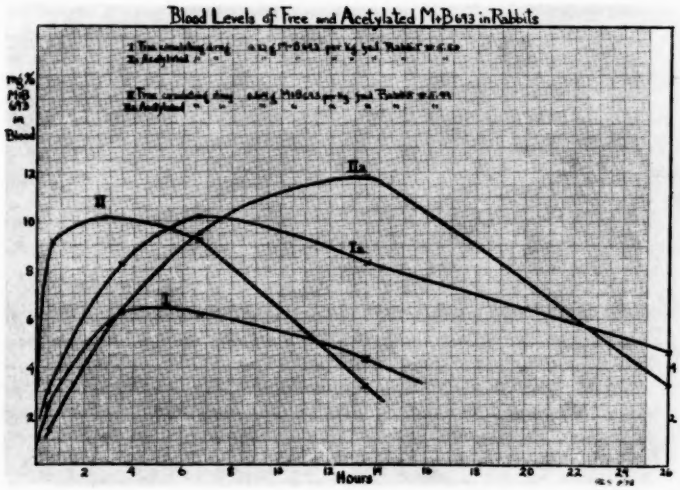

Fig. 2 Blood Levels of Free and Acetylated M+B 693 in Rabbits
I. Free circulating drug 0.32 g M+B 693 per Kg. fed Rabbit No. 5.50
Ia. Acetylated " drug 0.32 g M+B 693 per Kg. fed Rabbit No. 5.50
II. Free circulating drug 0.64 g M+B 693 per Kg. fed Rabbit No. 5.99
IIa. Acetylated " drug 0.64 g M+B 693 per Kg. fed Rabbit No. 5.99

Medical Association. As the drug circulates in the body it is conjugated with acetic acid, presumably by the liver, to form the compound having the constitution represented on the right. This compound is more insoluble than the free form and may be isolated in pure crystalline form in the urine of patients receiving the drug.

The amino (NH_2) group is also utilized in quantitative estimation of M & B 693. The method depends upon diazotization at 0°C. with nitrous acid and coupling with a suitable organic moiety to give a dye that may be compared colorimetrically against known standards. The conjugated form is determined after hydrolysis of a protein-free filtrate. This reduces the drug to the form on the left and colorimetric analysis is as above outlined. Since this procedure gives total circulating drug (free plus conjugated) the amount of drug conjugated is obtained by difference of analyses for the total and free drug.

Such analyses have been made on a number of rabbits receiving a single dose of the drug by stomach tube. Figure 2 shows the rate of

absorption, acetylation and excretion in two typical instances. Curve I gives the blood level of the free drug at varying intervals. It shows that the drug is immediately absorbed into the blood stream upon ingestion, appreciable blood levels being obtained within thirty minutes. In three to four hours a maximum is reached which is maintained for some three to four hours. Blood analyses twenty-four hours after ingestion show no free circulating drug. Curve Ia is the corresponding curve of the acetylated form. A definite lag is noted both in its initial and final phases. After twenty-six hours appreciable quantities of the acetylated form are still present in the blood.

Curves II and IIa for a rabbit on double the dose of curve I show similar results.

Table I shows the same type of analyses in tabular form made on patients receiving the drug over a usual course of therapy. Superscripts in cases 1, 2, and 3 indicate results of blood levels during initial phase of drug administration. Considerable variation in the acetylated values is noted. The second row of figures shows representative results of blood levels on the dosages given after a steady state had been obtained (usually forty-eight hours after initial dose). Case 4 is representative of the final phase and shows no free circulating drug twenty-four hours after the last dose.

The actual blood levels attained from a given dose are felt to depend on three factors: (1) the rate of absorption, (2) rate of acetylation and, (3) the rate of excretion. Evidence for the modifying effect of the rate of absorption is given in the first case, Table II. These were analyses on a patient with gastrointestinal obstruction which gradually cleared with consequent rise in blood levels. It is noteworthy that the per cent of acetylation remained approximately constant.

The ability of individuals to acetylate sulfapyridine varies between twenty-five and ninety per cent. Cases 2 and 3 of Table II are representative blood levels for patients with slight tendency to conjugate the drug.

The effect on blood levels of patients conjugating the drug to a high degree is given in the two comparative cases of Table III. Though both patients were on the same dosages, blood analyses made every three or four days reveal entirely different pictures: the free circulating drug in the second case is approximately three times that of the first. A possible explanation is to be found in the values of per cent acetylation which in the first case might be thought of as depressing the amount of free circu-

TABLE I

M+B 693 HUMAN BLOOD LEVELS

	Dosage *gm./diem*	Free *mgm. per cent*	Total *mgm. per cent*	Acetylated *per cent*
Case 1	5.5, 6, 6	5.5	5.5	0[1]
	6	10.5	14.2	30
Case 2	2, 2.5	2.5[2]	4.1	39
		1.2	3.3	64
Case 3	3, 3	2.0[3]	2.4	15
		3.7	6.5	43
Case 4	3, 3, 3	0.0	4.0	100[4]

Sample for analysis after:

1) 20 hrs. 1 gm. q4h
2) 10 hrs. 1 gm. q4h
3) 6 hrs. 1 gm. q4h
4) 24 hrs. after last dose

TABLE II

M+B 693 HUMAN BLOOD LEVELS

	Dosage *gm. per diem*	Free *mgm. per cent*	Total *mgm. per cent*	Acetylated *per cent*
Case 1	4, 3.5, 3	2.0	3.5	43
	3, 1.5	3.5	8.0	56
		5.5	10.5	48
Case 2	4, 3.5	3.0	4.5	33
	1.5	10.5	13.0	19
Case 3	5, 5, 2	7.5	10.0	25

TABLE III

M+B 693 HUMAN BLOOD LEVELS

	Dosage *gm. per diem*	Free *mgm. per cent*	Total *mgm. per cent*	Acetylated *per cent*
Case 1	3 gm daily for 22 days	1.2	3.0	60
		1.5	8.5	83
		3.0	10.0	70
		2.5	6.2	60
		1.5	6.5	77
		1.0	5.3	81
Case 2	3 gm. daily for 5 days	6.9	14.1	51

TABLE IV

M+B 693 IN URINE OF PATIENT

EXCRETION OF M+B 693

Dosage M-B 693 *gm. per diem*	Free *mgm. per c.c.*	Total *mgm. per c.c.*	Acetylated *per cent*	Daily Total *gm.*
4				
6	0.437	1.56	72.0	2.18
5	0.686	2.80	76.0	2.70
6	1.006	4.12	75.5	(.2)* +2.66
1	0.600	4.00	85.0	(.45)* +2.0
	0.00	0.16	100.0	0.12
	0.00	0.04	100.0	0.04

* Crystals of acetyl compound recalculated as free.

TABLE V

RELATION BETWEEN ACETYLATION AND EXCRETION OF M+B 693

	Total Drug given in gms.	*Acetylation per cent*	*Recovery in Urine per cent*
Case 1	16.5 in 8 days	30-40	82.5
" 2	22 in 5 days	30	72.5
" 3	22 in 5 days	55-65	57.5*
" 4	22 in 5 days	75-80	48.0
" 5	30 in 10 days	80-90	49.0
" 6	15 in 5 days	Variable due to renal shut-down	16.0

* Value low, as urinanalysis was stopped upon withdrawal of drug.

lating drug by conjugation. Urine analyses on this patient gave acetylation values of eighty-five to ninety per cent. Three months later the patient on the same dosage gave the same blood and urine analyses.

Table IV gives urine analyses for both free and conjugated forms. Constant values of acetylation again appear where presumably the rate of absorption is sufficiently high (first three lines of table).

In testing the efficacy of any new drug, it is important to know the amount excreted. Total urinary excretion varies considerably among patients as shown in Table V in which an inverse relation between amount of acetylation and excretion is found to exist in many cases. The per cent recovery of drug in Case 3 is low, as the urine samples were stopped on withdrawal of the drug. Other cases, not given here, on larger doses with the same per cent acetylation, appeared to eliminate relatively less in the urine. When renal activity is disturbed as in Case 6, very small amounts of the drug are recovered in the urine.

CONCLUSIONS

Blood analyses on seventy-five patients for sulfapyridine show:

(1) Sulfapyridine appears in the blood stream directly after ingestion.

(2) During circulation, the drug is detoxified by acetylation.

  (a) The amount of acetylation varies between twenty-five and ninety per cent.

  (b) This amount appears to be constant and characteristic for an individual.

(c) With abnormally low blood values of free drug are frequently found high acetylation values.

(3) The amount of circulating drug depends on three factors. Rate of absorption, acetylation and excretion. Acetylation appears to vary most among individuals giving rise to major differences in blood levels on given doses.

(4) Essentially all of the free sulfapyridine is eliminated in twenty-four hours; the acetyl form in forty-eight hours.

(5) Urine analyses confirm these findings. In addition fifteen to eighty-five per cent of the drug administered has been recovered in the urine. The variation appears at present to depend on (a) dosage, giving an inverse effect: the larger the dose, the less proportionally is found in the urine. (b) Renal activity: direct effect. The less the urine volume, the less the drug. (c) Acetylation: inverse effect: the less the acetylation the more the drug recovered in urine.

(6) Blood levels on adults receiving 3 gms. daily, normally show 4 to 6 mgm. per cent; those receiving 6 gms. daily, normally show 10 to 13 mgm. per cent.

THE TREATMENT OF DEPERSONALIZATION*

PAUL SCHILDER

DEPERSONALIZATION is a state of the personality in which the individual feels changed in comparison to his former state. This change extends to both the awareness of the self and of the outer world and the individual does not acknowledge himself as a personality. His actions seem automatic to him; he observes his own actions like a spectator. The outer world seems strange to him and has lost its character of reality. We find, therefore, in this picture changes of the self, or depersonalization in the narrower sense, and changes in the environment, or feelings of unreality, alienation of the outward world, "Entfremdung der Wahrnehmungswelt." For this latter phenomena, Mapother, Mayer-Gross,[1] Guttmann and Maclay[2] have suggested the term, derealization. Pictures of this type occur according to my own studies,[3] Haug[4] and Mayer-Gross[1] in a great variety of clinical conditions. The picture has been observed as a passing phenomenon combined with *déja vu* in the normal. It may appear in connection with organic diseases of the brain, especially before and after epileptic attacks. It has been observed in depressive psychoses and schizophrenia. In the beginning and in the phase of disappearance of severe neuroses it is not uncommon.

However, this picture occurs also as the dominant symptomatology of a very severe and chronic type of a specific neurosis. Patients of this type complain year after year about their changed experience concerning the self and the world. Cases are on record with a duration of twenty or thirty years. This study deals merely with this nuclear group, the neurosis depersonalization.

The philosophical and psychological interest which these cases offer is considerable. Taine[5] was the first to use the picture as proof for his philosophical theories of perception. Besides the complaints of changes in perception and emotions there are complaints concerning the experi-

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ence of one's own body and about changes in the perception of time and space. Accordingly, the philosophers have used every one of these complaints as proof that this particular function is the most important one in our relation to self, body and world.

The picture of depersonalization has also attracted the attention of psychoanalysts, among whom I may mention Sadger,[6] Nunberg,[7] Reik,[8] Federn,[9] Oberndorf,[10] Bergler and Eidelberg.[11]

The various authors have stressed different sides of the psychological problems. Reik stresses the constant self observation which according to his opinion is based on sadomasochistic attitudes. Oberndorf puts the main emphasis on the erotization of thought and especially upon the wish to adopt the way of thinking of the opposite sex. Other authors stress the exhibitionistic and voyeuristic components in the picture. Bergler and Eidelberg are of the opinion that there is a strong tendency to anal exhibition. This exhibition is transformed into an increased tendency to self observation. I am inclined to stress the fact that the patient with depersonalization has been admired very much by the parents for his intellectual and physical gifts. A great amount of admiration and erotic interest had been spent upon the child. He expects that this erotic inflow should be continuous. The final outcome of such an attitude by the parents will not be different from the outcome of an attitude of neglect. Dissatisfaction has to ensue even if the parents live in a state of continual admiration of the child since every such relation does not consider the child as a total human being but merely as a show piece. The dissatisfaction and deprivation of the child has to express itself in an increase of aggressive and submissive tendencies. These combine with sexual tendencies to sadomasochism. Finally, by identification with the parents, self observation will take the place of the observation by others. The self observation will be blended with sadomasochistic tendencies. The individual will at first be able to admire his body as well as his thinking. Since such a detachment from the love object cannot remain satisfactory, the self adulation will be followed by hypochondriac signs. To the denial of vision in the sphere of perception is now added the loss of admiration of one's self. The individual, however, does not completely give up and will at least enjoy the self observation which represents the sadistic components as well as the voyeuristic and narcissistic (self-admiring) ones. The patients, furthermore, preserve their intellectuality in this way and are able to continue their activities in the social and physical world which

may appear outwardly successful although empty of emotional satisfaction for the individual. Depersonalization is the neurosis of the good looking and intelligent who want too much admiration.

It is understandable that a neurosis of such depth will need a psychotherapy of long duration. The best observers in this field agree on this point. Oberndorf, for instance, has treated his cases for a long time and Bergler and Eidelberg write as follows: "We think that this absolute pessimism (concerning the treatment) is not justified; however, it is a prerequisite for the therapy that one knows the mechanisms and starts on the right point. Furthermore, very long time is necessary. While the analysis of a more severe case of obsession neurosis takes at least two to two and one-half years, the double space of time is the requirement for the treatment of depersonalization. It does not seem to be very hopeful if one demands half a decennium for a treatment. However, '*amicus Plato, magis amica veritas.*' " The experiences of Oberndorf and myself are, however. better. Some of my cases were treated with individual psychoanalysis, some of them were treated in group psychotherapy. Two cases may be mentioned shortly.

Rose H. came for treatment at the age of twenty-five with depersonalization symptoms which had existed for two years. She was good looking and of superior intelligence. As so often occurs, the symptoms had suddenly started during an episode of petting in which she had felt that she had lost herself and her emotions. Her sexual feelings also vanished suddenly. This episode had followed an incomplete and disappointing love affair with her employer. The final rejection by him had revived the humiliations she had experienced in early childhood from her father. The psychological treatment led to a recovery after two years. The symptoms disappeared completely; however, one year after the treatment, the patient had not yet made a sexual adaptation.

Gertrude W. came for treatment at the age of twenty-one. Depersonalization symptoms had persisted for several years. She complained "that things were moving up and down before her eyes." "I feel my head is empty. There is only a blank inside. . . . It is as if I would be asleep all the time. I do not realize how time passes. My whole intelligence and personality have disappeared. I have no desires anymore. I might as well be dead. . . . My voice has changed completely. Sensations are present but they do not reach my head." The patient had also a wealth of hypochondriac sensations which pertained particularly to her abdomen. She

was very much concerned about her anal functions. A great hostility concerning the mother reached back into early childhood. There were very lively sadomasochistic phantasies since the age of five. The patient was treated with group psychotherapy and lost almost all her symptoms; however, in this case, also, no sexual adaptation was reached.

Three other depersonalization cases were treated by L. Bender with good results. However, several years later all three cases relapsed under difficult outward situations. In one of my cases no therapeutic result was achieved in three months and the patient discontinued the treatment. In two cases psychotherapy resulted in minor gains. These cases will be mentioned later in another connection.

We may summarize by saying that psychotherapy in depersonalization cases takes a great amount of time, is technically difficult, does not always remove all problems and does not protect the patient from relapses. However, there is no question that every case of depersonalization needs a great amount of psychological help, and there is no reason to be pessimistic concerning psychotherapy in these cases. The treatment has to be psychoanalytic or has to utilize psychoanalytic insight.

Considering the difficulties of the psychotherapeutic approach, one might ask what could be done for these patients by medication. I have occasionally tried benzedrine in depersonalization cases; however, the results were passing and the psychotherapeutic approach was in no way helped by the medication. Guttmann and Maclay[2] have studied the influence of mescaline on depersonalization symptoms insofar as they consist of changes of the surroundings (derealization) but not of the self. However, this improvement was of short duration, not lasting longer than one day. The authors come to the conclusion that it may be used as an adjuvant for psychotherapeutic activity. A drug which brings a relief of short duration is obviously not of a great therapeutic value with such chronic problems. It is usually not very helpful in psychotherapy when one proves to the patient by the temporary relief with drugs, that he can feel better. Drugs which allow the patient to come to a deeper insight by increasing the transference situation and changing the state of consciousness help the psychotherapeutic approach much more than drugs which merely relieve symptoms. Sodium amytal may act in such a way. It has not been tried in depersonalization cases. I have, myself, tried to use benzedrine[12] as a help in revealing psychotherapy of neuroses. However, as mentioned above, such results were not achieved in depersonalization cases.

The modern methods of treatment for schizophrenia have only been tried occasionally in severe neuroses. Glueck[13] mentions in one of his publications a case of severe obsession neurosis which improved by insulin treatment. In the series of cases treated in Bellevue, one case of severe obsession neurosis reacted only temporarily to the treatment. At Bellevue we generally found the application of metrazol therapy simpler from a technical point of view[14] and decided, therefore, to make an attempt to treat this particular type of neurosis with metrazol. The depersonalization cases constitute a comparatively well defined group of neuroses. The psychotherapeutic approach to these cases is difficult. Results obtained in such a group with metrazol might be of use in evaluating the treatment for neurosis in general. We have followed the technique of Meduna[15] and use a 10 per cent aqueous metrazol solution. Injections were given intravenously in doses varying from 4½ to 15 grains. We tried to produce three convulsions in a week. One case may be reported in a short abstract, as an example.

Johanna L., thirty-one years old, comes from a family in which the father and one aunt had severe psychotic states probably of manic-depressive character. She was always considered an outgoing personality. Also her brothers and sisters were energetic and successful. She was the oldest of five children, three girls and two boys. She had two children, one of whom was only a few months old when the patient got sick. The family was at that time in straitened financial circumstances. The illness started five months before admission to Bellevue Hospital. She complained that she always felt too tired and was disinclined to sexual intercourse. She ate very little and claimed that she had lost her sense of taste. She thought this was as a result of a cold. She became untidy in appearance and was preoccupied with the care of her children. She complained that she had lost interest in things; that she didn't belong to this world and that she couldn't cry. She was sent to a sanitarium. There she stated that she was not alive but had turned to stone and had no feelings and no emotions. In the sanitarium she swallowed several needles with suicidal intent, and was, therefore, sent to Bellevue Hospital, on September 10. She said: "I can't live, I don't feel at all, I just got fear of life, everything became complicated, everything turned in me, the whole world just looks flat. Nobody can help me. It feels as if I had no place on earth; nothing in the world belongs to me; I don't feel that my family and children belong to me; life has been taken out of me; I seem to be inside out.

Everything looks backward; the heart doesn't seem to be in the same place; I can't change; just like a chair over there. It is as if the eyes would look inside instead of out. Time neither passes nor stands still. It doesn't seem like another day; there is no penetration of enjoyment. My mind goes round and round all the time in circles; the whole world looks flat to me. I know what torture you and everyone else is going through but no torture is greater than my misery." On the ward she was seclusive and did not talk spontaneously. However, she was very productive when one talked with her. On one occasion, she tried to grab iodine in order to drink it.

On October 4th, metrazol treatment was instituted. She received 4½ grains intravenously and had no convulsion. From then on, up to the seventh of November, fifteen convulsions were produced; the first four with injections of 6 grains, the subsequent three with 7½ grains and the last eight with 9 grains. There were no particular incidents during the treatment. The improvement started after the third convulsion and progressed steadily. The clinical symptoms had practically disappeared after the tenth injection. The patient was discharged fully recovered and with full insight, but she still receives psychotherapeutic help.

We have treated nine cases so far. Table I shows the most important features of these cases. The patients were treated in the hospital with the exception of two who were treated in the out-patient department. These two patients, however, could not be induced to have more than three convulsions. They felt improved but experienced a sensation before the convulsion so terrifying that they did not want to continue voluntarily. We have had the same experience in other patients whom we tried to treat in the out-patient department. We have discussed all the details of the treatment, not only with the patients, but also with the relatives and treated only those patients who could themselves be convinced that the treatment might be effective. There were no untoward incidents in the treatment, except that one patient dislocated his shoulder, but the effects of this had disappeared in a few days.

Not much has to be added to this table. Everyone who has worked with depersonalization cases will agree that the results surpass the results reached by other methods. One may doubt the diagnosis in the one or the other case, for instance, in the case in which emotional flatness is noted. This case was diagnosed by others as one of schizophrenia. The borderline between endogenous depression and depersonalization may be

TABLE I

NINE CASES OF DEPERSONALIZATION TREATED WITH METRAZOL

Name	*Age*	*Additional Symptoms*	*Duration Before Treatment*	*Previous Psycho-therapy*	*Number of Convulsions*	*Maximal Dose in Grs.*	*Result*
J. L.	31	Suicidal attempts Severely depressed	5 months	Incomplete	15	9	Cured
R. O.	29	Slight residual signs of previous encephalitis	Several weeks	None	9	9	Cured
L. R.	31	Severe psychological conflicts for years	4 months	Incomplete	10	15	Much improved
S. H.	30	Neurotic conflicts preceding suicidal attempts	1 year	Incomplete	7	7½	Improved
B. A.	19	Catatonic pupils	3 months	None	8	13½	Cured
S. S.	32		4 years	Moderate improvement	3	10½	Further but still incomplete improvement
S. R.	18	Hears his own voice continually as obsession	15 months	None	25	12	Improved
W. T.	23	Flatness of emotions	4 years	Incomplete	22	10½	Slightly improved
A. S.	26		4 years	Partly successful	3	10½	Further but still incomplete improvement

sometimes difficult to draw. However, these diagnostic difficulties lie in the nature of the subject.

It is obvious that insulin and metrazol treatment have a field of application also outside of the field of schizophrenia. They have been variously tried in manic-depressive psychoses. My own experience with the metrazol treatment of manic depressives is too small; however, there were startling results in two cases of confused mania (the only ones treated). I have also observed improvements in depressions. Bennett[16] reports that ten consecutive severe depressive psychotic patients have all been relieved by shock therapy. He reports that the improvement started two weeks

after the treatment began. He also quotes literature which asserts that hysteria and anxiety cases derived benefit from metrazol treatment insofar as the patients established a better *rapport* for psychotherapy after its use.

In most of our cases the first signs of improvement appeared after the first three or four injections, and in the majority of cases the symptoms disappeared after about six to ten injections. We find it advisable, however, to give two or three more injections after the symptoms have cleared up. The symptoms may disappear without further psychotherapy; even then, the individuals always have unsolved psychological problems. I am, therefore, of the opinion that every depersonalization case which is treated with metrazol needs extensive psychotherapy even after he is free from manifest symptoms. We have acted accordingly in all cases in which the outward circumstances made the application of psychotherapy possible. This is the same point of view which Orenstein and myself[17] have taken in respect to insulin and metrazol treatment of schizophrenia.

One may, of course, raise the question whether the results of this treatment of depersonalization are merely due to psychological factors connected with the treatment. The patient experiences indeed terror and fright and even a threat of death. The transference is increased when he regains consciousness. However, it seems to me that such psychological phenomena are obviously the reflection of deep-lying changes in the organic functions. Furthermore, experience shows that deep-lying neurotic pictures cannot be influenced by mere fright. I am, therefore, of the opinion that organic changes in the brain function connected with metrazol treatment have a therapeutic effect on the depersonalization neurosis. It is not possible to say at the present time whether one can generalize this statement for other neurotic conditions. It is even too early to state that the cure in depersonalization cases and in manic-depressive psychosis and schizophrenia will be a lasting one. However, one of my recovered depersonalization cases is free from symptoms and has worked steadily for more than ten months.

Summary and Conclusions

1. The picture of depersonalization is a rather well circumscribed chronic neurotic picture which offers great difficulties for psychotherapy. However by psychoanalysis or methods akin to psychoanalysis good

results can be obtained if the treatment is continued for years.

2. Treatment with mescaline and benzedrine is ineffective.

3. Nine cases are reported in which the intravenous treatment with metrazol in doses sufficient to give convulsions, gave good results. However, some of the cases were not completely cured.

4. This treatment should be combined with psychotherapy.

5. The effects of treatment are probably due to organic changes. The psychological effects of the drug treatment are not sufficient to explain the results.

6. Metrazol treatment is not only effective in schizophrenia but also in manic-depressive pyschoses and in specific types of chronic neuroses. The question arises whether other types of so-called psychogenic disturbance (neurosis) will be responsive to this treatment.

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Discussion

MANFRED SAKEL

The paper of Dr. Schilder is one of great interest. It is indeed an important step in the endeavor to treat neuroses somatically. I do not dare to discuss the psychological aspects of depersonalization since Dr. Schilder is one of the most experienced in this matter. No doubt those who expect me to defend the wholly somatic point of view will be disappointed. It is therefore fortunate that there is no need now for such a dualistic defense.

Depersonalization should be considered as a kind of dysfunction in the perception of the own personality. This definition by itself brings up a very difficult question. To discuss the related problems would force me to define the meaning of the term "personality," itself. I do not wish to involve myself in these far-reaching spheres. I may only call your attention to the fact that there are symptoms in many other diseases which could easily suit this group. These are diseases which, it is generally assumed, do not derive from psychologic sources only. I would like to emphasize the fact that similar experiences occur in the onset of schizophrenia, as Dr. Schilder mentioned. The schizophrenic often feels himself estranged from the external world, and the surrounding environment has a changed significance to him. He perceives new, peculiar and quaint features which he did not notice before, from without as well as from within.

It seems to me that the normal picture of the world and the feeling of being familiar with it, as well as a feeling of being familiar with one's own psychological condition, should be always considered as bound to normal functions of the brain. It seems to me too that every change in the organism and especially in the functions of the brain is perceived in some way by the individual self. One may imagine it as a kind of a switchboard on which the red-lights can be flashed only when disturbances occur which bring them to our perception, but normally there is no realization at all because no red-light flashes occur.

These warning signs may come from two different sources: From the pathways of perception (when confusion or "short-circuiting" result in hallucinations); and secondly, from disturbances of self-perception. These experiences are both an expression of the dysfunction of the brain.

This statement does not exclude the fact that this dysfunction can be and frequently is induced by psychological causes. One recalls the known example of the cat which shows stormy intestinal movements while stroked in the wrong direction. Everyone will admit that these movements are, in the final analysis, induced by biochemical stimulation. Doubtless everyone will admit also that the releasing cause was the feeling of discomfort. The culmination of this result can be achieved from both poles.

I may stress that some cases of neuroses have a special tendency for biochemical dysfunction. A slight psychological cause is sufficient to release the symptoms. Dr. Schilder at the end of his paper pointed out that somatic changes are finally and basically responsible for neurotic symptoms. Although there are further additional questions which unfortunately cannot be thoroughly discussed in brief, this is the point in which I generally agree with him. May I add that at the beginning of the pharmacological shock treatment of psychoses, I treated a great number of patients including almost all diseases within the psychiatric range. It happened that I was able to treat among them quite a number of those with symptoms of depersonalization. It is true that the results were most satisfactory, however, I did not publish the results, being afraid that I would be charged with claiming to possess a cure for all maladies.

It is regrettable that Dr. Schilder did not have the opportunity to watch the development of this shock treatment from the beginning. I recognized very early, that the production of convulsions, *per se*, is not efficient enough a factor, in the combined therapeutic procedure to be used alone effectively. Although administration of metrazol without insulin is certainly easy, no advantage could be seen either for the doctor or for the patient. For this reason I treated also the patients with obsessional neuroses and patients with symptoms, as described principally by Schilder in the usual way. I used the metrazol to provoke the imminent convulsion in hypoglycemia about two to three hours after the application of insulin. The terrifying effect of the preconvulsion period was entirely eliminated. In our cases no fears were observed, therefore no objections were made, and no necessities occurred to stop the treatment. But this is relatively of less importance. Mainly I would like to point out my belief that the effect in quality and also in the duration was much better by applying the treatment as I described it.

In these cases the metrazol doses to provoke a convulsion during the

hypoglycemia average about one-third of the doses which Dr. Schilder mentioned; this factor is not to be neglected. In some patients, who did not show depersonalization symptoms at all during their illness, these symptoms were manifested in a marked degree for a short time after the patients' awakening from coma. An obsessional neurotic, for example, reacted in this manner and one patient with schizophrenia whom I described in my book. I did not keep records of the duration of improvement in cases of neuroses and so cannot say much about this; but in two patients whom I treated in the above-described manner, I was informed of progress for a period of two years. One was an executive who had to neglect his business for a few years due to his illness. After the treatment he was able to assume again the responsibility of his business and, as I was told, very successfully. He was still doing so when I last heard of him.

Discussion

Louis Wender

Since Dr. Schilder's paper deals with the treatment of depersonalization, I shall not enter into the psychodynamics of this disorder and its treatment by psychotherapeutic means alone. There is no doubt that there are underlying psychological factors in this symptom complex. Depersonalization, *per se*, is not a disease entity, but a symptom prevalent in many mental disorders. It is common in schizophrenia and manic-depressive psychoses, and also in chronic psychoneuroses. Although each individual may describe his symptoms somewhat differently, the concurrent syndrome is that the outer world seems strange; there is a feeling of unreality and an estrangement from the outside world. There is a loss of "feeling tone." This symptom is so common among hospital patients with functional disorders that one is at a loss, at times, to overcome it even with intensive psychotherapy. Dr. Schilder tonight has demonstrated to the Society the fact that depersonalization, whether as a symptom alone or associated with other symptoms of mental disease, can be overcome by the use of chemotherapy.

At Hastings our experience with metrazol has given us the same results as those reported by Dr. Schilder. We have administered metrazol to forty-three patients, completing the course with thirty-six. Twenty-

one of these were suffering from chronic psychoneuroses and depressions in which the depersonalization syndrome was very marked. Of the fifteen others manifesting a schizophrenic reaction, only a few presented any depersonalization symptoms. Our results were very satisfactory. As a matter of fact, we are of the opinion that in depressions where the stupor is not very deep, where there is no retardation, but where there are marked symptoms of depersonalization and feeling of unreality, metrazol has a very beneficial effect in accelerating the rate of recovery. The common statement that depressions get well anyway, even without chemotherapy, is probably true, but metrazol precipitates an earlier recovery and perhaps breaks up the manic-depressive cycle. I make this statement on the basis of our experience with two patients, both manic-depressives, one with obsessional thinking, one with a depersonalization syndrome. The latter had two previous attacks, each lasting about a year; the other was also sick previously for about nine months. In each case the depression was followed by a hypomanic phase. Both recently had a recurrence of their episodes and were hospitalized, and we decided to give metrazol to both. To our great surprise both cleared up rapidly, the duration of hospitalization in one case being seven weeks and in the other, about ten. One left the hospital in July and the other in September; neither showed subsequent hypomanic reactions and both are doing well at present. This, of course, requires further study and verification.

I am in agreement with Dr. Schilder that metrazol and insulin are not the only remedies in the treatment of the chronic psychoneuroses; that these persons require psychotherapy and that the psychotherapy should be started as soon as the patient begins to show response to the chemotherapy; that furthermore, the administration of metrazol should not be discontinued suddenly but should be reduced gradually. In our experience at Hastings, after the patient begins to show definite improvement, the treatment is reduced at first from three times a week to twice a week and later to once a week, the patient in the meantime receiving intensive psychotherapy. After the injections are completely discontinued, active psychotherapy is continued until the patient is discharged. We believe that this prevents a recurrence of the mental disorder. Thus far, none of the metrazol cases in our group that recovered or showed improvement have returned to the hospital.

How metrazol works I am unable to state. Personally I do not think it is a fear phenomenon, for our experience has shown that if the patient

does not get a good convulsion, he does not show the proper response, and the patient's fear when there is no convulsion is much greater than when the patient gets a seizure. As a matter of fact, the fear of impending death is so marked if there is no convulsion that the patient sometimes refuses to take another injection unless he is promised that the dose will be large enough to give him a convulsive seizure. Repeated injections without convulsions do not produce any change. On the other hand, if there is going to be a response, one notes an improvement after the third or fourth consecutive convulsion. Therefore, if we are going to assume that the reaction is due to fear, this fear probably touches the deep unconscious, but certainly it is not conscious fear that gets them well. The probabilities are that the metrazol seizures disturb the biochemical relationship in the system, perhaps discharging certain toxins and reorganizing the cortical functioning.

Our experience has also shown that metrazol can be used in severe chronic psychoneuroses, especially of the obsessional type, or the chronic anxieties. At present we have a patient, a severe compulsion neurotic of three years' duration, who prior to coming to Hastings received psychoanalytic treatment for ten months and was just able to get along. When admitted to the hospital, he was so full of obsessions and compulsions that it would take him hours to dress and undress. It would take him a whole half hour to wash his hands. He was afraid to touch anything and even to say anything because he was afraid that his words might hurt someone. He was so obsessed that he even felt his very presence might hurt people and, as a result, he would stay in his room for hours at a time before he would decide to go out. When the family wanted him to go out of the house, they resorted on several occasions to putting some strong disinfectant in his room in order to choke him out. This patient received eighteen metrazol injections and by the time he had had the twelfth, we were amazed to note the change in his condition. Practically all the obsessions enumerated above have disappeared: he even works around the hospital, cleaning, uses his hands freely and enters readily into conversation. This patient is at present under active psychotherapy in order to try to remove some of the deeper underlying mechanisms in the hope that we may change his character thinking.

Dr. Schilder should be congratulated on bringing this interesting topic and this form of treatment before the Society, for there are a great many patients whose financial status does not allow them the luxury of

undertaking an analysis of a year or two in the hope of getting their difficulties adjusted, and there are also many people whose intellectual constitution is such that, even if they can afford the money, analysis is of no avail. We who practice among the former group have to resort to various means of getting them back to society, and if metrazol can remove the symptoms and make the individual a useful member of his social group, it should be tried on all patients who fail to respond to psychotherapy or in whom the duration of illness is over a year.

PRESENT STATUS OF PROTAMINE INSULIN*

HERMAN LANDE

THE effective retardation of the action of insulin by combination with protamine promised a new era in the treatment of diabetes. The demonstration that the addition of zinc to this compound not only increased its stability but enhanced its hypoglycemic value resulted in the preparation now in general use. Protamine zinc insulin has been available commercially for two years. The early enthusiastic reports have been somewhat tempered by further experience but in the light of that experience we are better able to evaluate its advantages and disadvantages. The prolonged action of protamine insulin has been amply confirmed and careful studies in fasting patients have indicated that it may be effective for as long as forty-eight to seventy-two hours. Obviously a more stable blood sugar level can be maintained than with a soluble insulin whose activity is limited to approximately six hours. There is, however, an important distinction between the availability of protamine zinc insulin throughout the twenty-four hours and the physiological action of the normal pancreas. Unfortunately, insulin is liberated from the subcutaneous depot of protamine zinc insulin at a constant rate independent of the physiological requirements of the body, even after the ingestion of carbohydrate.

Reports from large groups throughout the country disclose a marked variance in the results obtained with protamine therapy, ranging from 30 to 80 per cent of satisfactorily controlled cases. However, it should be borne in mind that statistical studies of diabetes are especially misleading. Diabetics differ in their response to treatment and clinics differ in their criteria of satisfactory control. In fact, one of the most disconcerting results of the introduction of protamine zinc insulin has been the lowering of the standards of diabetic control.

The varying response of diabetics to treatment is of especial importance in evaluating the results with protamine zinc insulin. The obese

* Delivered December 21, 1938 at the joint meeting of the Section of Medicine and the New York Diabetic Association.

adult type is as a rule easily controlled by dietary restrictions with or without the use of insulin. A moderate dose of protamine zinc insulin given once a day is often sufficient to maintain a persistently sugar-free urine and a fairly stable blood sugar level in adults who have been previously controlled by thirty units or less of regular insulin. Protamine zinc insulin is an almost ideal therapeutic agent for this group of patients so far as convenience and control of glycosuria are concerned. Fortunately, the great majority of diabetics are of this type.

The juvenile, adolescent and early adult diabetic have frequently presented difficulty in treatment because of the irregular control of glycosuria and the tendency to severe hypoglycemic reactions. The use of protamine zinc insulin in this group has been less encouraging, and satisfactory control can only be obtained in a small percentage of cases with a single dose of protamine zinc insulin. The general consensus, however, is that the results are superior to those obtainable with regular insulin.

The latent period of soluble insulin varies from fifteen minutes to one hour and its maximum duration of action four to six hours. Protamine zinc insulin begins to exert its maximal action after three hours and this action may be prolonged from twenty-four to forty-eight or even seventy-two hours. Regular insulin is therefore best adapted for the control of postprandial hyperglycemia and glycosuria. Because of its limited time of action it will be of little value in the control of the increasing nocturnal hyperglycemia which characterizes the severe diabetic. Protamine zinc insulin liberated at the rate of 3 to 4 per cent an hour from its subcutaneous deposit will control the nocturnal and fasting hyperglycemia but will not be available in amounts adequate for the hyperglycemia that follows meals. It should be emphasized that the primary objective of treatment with protamine zinc insulin is the control of the disease during the night. Experience has demonstrated that this can be best accomplished by a single dose of protamine zinc insulin one hour before breakfast. The maximum effect on the blood sugar is exerted twenty to twenty-four hours after its administration. By administering protamine zinc insulin before breakfast, it is therefore possible to utilize a single specimen of urine, that passed before breakfast, as a reliable guide to dosage. If the specimen before breakfast is sugar-free for three to four days, a blood sugar determination should be made regardless of the degree of postprandial glycosuria. Under no circumstances should the

dose of protamine zinc insulin be increased to control the postprandial glycosuria in the presence of a normal fasting blood sugar level. Such a procedure may result in serious hypoglycemic reactions. Furthermore in establishing the dosage of protamine zinc insulin, changes in diet and medication should only be made after three or four days as there is reason to believe that protamine zinc insulin may exert a cumulative effect for as long as seventy-two hours.

With the dose of protamine zinc insulin established by the fasting urine specimen and blood sugar level, a persistent postprandial glycosuria can be controlled by one of two methods: (1) by supplementary doses of regular insulin or (2) by modifications of diet. The supplementary use of regular insulin means multiple injections and in this way one of the main advanatges of protamine zinc insulin is lost. However, multiple injections may be necessary in those cases that cannot be adequately controlled by dietetic methods. It has been our experience that protamine and soluble insulins cannot be combined in the same syringe, as protamine zinc insulin contains an excess of protamine that will partially precipitate the soluble insulin.

Our experience has agreed with that of Wilder, Joslin, Campbell[1] and others that better control is usually obtained if not more than 150 grams of carbohydrate are included in the daily allowance. Others have reported satisfactory results with as much as 300 grams of carbohydrate daily but in most cases the disproportion between the insulin available and the large carbohydrate intake at meals creates difficulty in control. After all, the usual diet of 150 grams of carbohydrate (70 of protein, and 80 of fat) permits three slices of bread, a large portion of oatmeal, three portions of fruit, four portions of 5 per cent vegetables, one-quarter pint each of milk and cream, an egg, two moderate portions of meat and three portions of butter.

The usual difficulty in treating the severe diabetic with protamine zinc insulin is the tendency to postprandial glycosuria, especially after breakfast, and the tendency to hypoglycemia during the night and in the early morning. The most common method of overcoming postprandial glycosuria is to spread the meals, witholding portions of carbohydrate for afternoon and bedtime feedings. To overcome marked fluctuations in the blood sugar level we have attempted to regulate the diet so as to retard the absorption of glucose and in this way prevent the flooding of the blood and tissues with sugar after meals. By this method

we have hoped to strike a more even balance between the glucose available for oxidation and the insulin liberated from its subcutaneous depot. Dr. Pollack[2] has demonstrated that carbohydrates differ in their relative rates of availability as glucose. This is especially true of fruits. For all practical purposes fruit juices represent almost pure glucose solutions which are rapidly absorbed and cause a sharp rise in the blood sugar. On the other hand, such a fruit as the banana is slowly absorbed and produces a less marked elevation of blood sugar. The addition of fat in the form of heavy cream to fruits and cereals delays the emptying of the stomach and retards still further the absorption of glucose thereby prolonging its availability. The advisability of a small breakfast is suggested by the common tendency to glycosuria after this meal.

The problem of avoiding nocturnal and early morning hypoglycemia requires a constant supply of glucose during the night. It is known that from 50 to 60 per cent of protein is convertible into glucose and that the emptying time of the stomach after a meat meal may be as long as three hours. For protein to become available as glucose it must be digested, the amino-acids carried to the liver, deaminized and resynthesized into glucose. The time necessary for these processes prolongs the availability of the glucose derived from protein. This suggests the advisability of a large meat meal at night and the serving of the evening meal as late as possible. In accordance with these observations we have adopted the following dietetic regime for use with a single dose of protamine zinc insulin administered before breakfast.

1. Diets are limited to 150 grams of carbohydrate at the onset.
2. The use of readily absorbed fruits and fruit juices is avoided.
3. Carbohydrate is divided into 1/5, 2/5, and 2/5 for breakfast, lunch and supper.
4. Proteins are divided into 1/6, 1/6 and 2/3 for breakfast, lunch and supper.

With this regimen we have usually been able to avoid the necessity of supplementary feedings and to control the tendency to nocturnal hypoglycemia.

However, in spite of all dietetic methods an appreciable postprandial glycosuria frequently develops in the presence of a normal or even subnormal fasting blood sugar level. At times the glycosuria will appear and disappear for no detectable cause. More often the cause will be found in errors of technique in the administration of protamine zinc insulin. To

evaluate a case properly the history of the actual vial of insulin used must be known. Many jobbers and retail druggists keep the protamine zinc insulin on the open shelves of a hot storage room for a variable period of time with consequent damage to the insulin. Even if the patient who buys the insulin is as careful as possible the damage has already been done. In addition the storage of insulin on the window sill, the small gauge needle, the droplet of alcohol accidentally put into the insulin vial and the hot syringe may contribute to failure in therapy. The frequent development of subcutaneous indurations at the site of the injections suggests that irregular absorption may also be an important factor. A varying percentage of cases, however, cannot be controlled with protamine zinc insulin according to the usual standards. There is no doubt that a fair proportion of patients taking protamine will not be as nearly sugar-free throughout the twenty-four hours as when taking three or four doses of regular insulin a day.

This raises the important question of the criteria for adequate control. These range from the insistence upon a normal blood sugar throughout the day to the other extreme that no attempt should be made to restrict the diet or control glycosuria but to administer protamine in doses adequate to prevent ketonuria. It may be possible to prevent hyperglycemia throughout the twenty-four hours by the administration of soluble insulin before each meal in addition to protamine zinc insulin in the morning. However in the majority of even moderately severe cases an attempt to maintain a normal blood sugar throughout the day will result in frequent hypoglycemic reactions. Joslin[3] has recently stated that the restriction of the loss of sugar in the urine to 10 per cent of the carbohydrate in the diet is justifiable. According to the dietary regime used by Joslin and the average urinary excretion, this approximates a 1 per cent glycosuria. We have considered a fractional glycosuria after meals with no more than an occasional trace of sugar in the urine before breakfast as satisfactory control. In evaluating standards of control, a distinction must be made between the glycosuria which follows a meal and that which occurs during the night. The former represents an overflow from an exogenous food supply; the latter is derived from the stores of glycogen and the breakdown of endogenous protein. There are periods during the twenty-four hours when the tissues of the severe diabetic treated with insufficiently frequent doses of unmodified insulin deliver amino-acids for the manufacture of dextrose. This results in recurring periods of negative

nitrogen balance and an accompanying ketosis. Wilder[4] has demonstrated that even in the presence of an appreciable postprandial glycosuria, the endogenous production of glucose and the resulting protein wastage can be prevented by protamine zinc insulin. Furthermore, the absence of ketosis during the twenty-four hours is much more complete with protamine zinc insulin than was ever possible with three or even four doses of soluble insulin in cases of severe diabetes. The nitrogen sparing and antiketogenic effect made possible by the continuous action of protamine zinc insulin is the basis for the relaxation of standards of diabetic control and the abandonment of a consistently sugar-free urine as the essential aim of diabetic therapy.

One of the fundamental concepts of diabetic therapy has been that an uncontrolled glycosuria increases the susceptibility to the untoward complications of diabetes. This is especially true of the young diabetic where the clinical picture is not complicated by senile degenerative changes. In the adult, tissue susceptibility in the presence of glycosuria is probably best illustrated in infections which remain refractory to treatment until the diabetes has been controlled. Coma has in large part been eradicated as a cause of diabetic mortality and our therapeutic problem today is the prevention of the degenerative changes to which the diabetic is particularly susceptible. It may be that with the prevention of acetonuria and protein wastage, the degree of glycosuria is of no significance in the production of degenerative changes. The cause of these degenerative changes is not known and the evidence that hyperglycemia and glycosuria are etiological factors in their production is not convincing. Eventually we may be able to state that glycosuria with protamine zinc insulin is not harmful because there is always functioning insulin in the body, a status not attainable with soluble insulin. However, even though a continuous supply of insulin is available and protein wastage and acetonuria can be prevented by protamine zinc insulin, the prevention of degenerative changes in diabetes is far too serious to be dismissed with the assumption that a persistent glycosuria is harmless without more convincing evidence than has as yet been presented.

The most serious complication encountered in the use of protamine zinc insulin is the hypoglycemic reactions. These are especially malignant in that the hypoglycemia develops gradually and is not attended by the stormy symptoms characteristic of regular insulin. If the patient is confined to bed or is resting, symptoms may be entirely absent or appear

late. It is a common experience to encounter a patient completely symptom free in spite of a blood sugar of 30 or 40 mgms. When symptoms appear they are characterized by drowsiness, fatigue, headache and nausea. They are often overlooked at the onset, especially as they may occur at a time when the patient cannot believe that the initial warning symptoms are of hypoglycemic origin. Because of the slow fall in blood sugar the compensatory mobilization of epinephrin is less pronounced and the tremor, sweats, tachycardia and throbbing sensations that characterize the reactions with regular insulin do not appear. Furthermore, the hypoglycemia may recur after treatment or even after meals. Sugar should therefore be administered at half hour intervals for a prolonged period and should be immediately resumed if symptoms recur. Because of the absence or paucity of symptoms and the danger of insulin reactions with protamine zinc insulin, patients should not be dismissed from observation if the fasting urine contains no sugar unless the blood sugar has been determined. Another important factor to be borne in mind is the hypoglycemic effect of muscular exercise in the presence of protamine zinc insulin. Most of the severe reactions which have been reported have followed undue exertion. It is therefore necessary to regulate the amount of physical activity and to administer carbohydrate before and after exercise to neutralize the depressing effect of exertion on the blood sugar. Furthermore, there is experimental evidence to indicate that severe, prolonged hypoglycemia may produce permanent pathological changes in the central nervous system.

There is usually no difficulty in starting ambulatory patients on protamine zinc insulin but the transfer of patients long accustomed to regular insulin to protamine zinc insulin may be associated with serious difficulties. One of the few cases of coma that we have seen during the past year was precipitated by the abrupt transfer of a moderately severe diabetic from regular to protamine zinc insulin without the use of supplementary doses of soluble insulin. It does not seem that the difficulties encountered can be entirely explained by the fact that the full effect of protamine zinc insulin is available only after seventy-two hours. In the light of my personal experience, I do not believe that a severe diabetic should be transferred from regular to protamine zinc insulin without hospitalization.

In the preoperative and postoperative care of surgical diabetics and in the treatment of diabetic acidosis and infections, protamine zinc

insulin has proved of value. Protamine zinc insulin can be given with comparative safety several hours before an operation for by the time it becomes effective the need for it will have arisen. One-half to two-thirds of the usual dose may be given on the morning of the operation. Any glycosuria that may develop after the operation can be controlled by regular insulin. The daily use of protamine zinc insulin, supplemented if necessary by regular insulin, can be continued during the postoperative period until the patient is ready to resume his regular regime. Protamine zinc insulin may also be used in the treatment of diabetic acidosis and coma. The patient may be given a large dose of protamine zinc insulin at the beginning of treatment and regular insulin then administered for the next three or four hours as though the protamine zinc insulin had not been given. Similarly in infections the patient may be given his usual maintenance dose of protamine zinc insulin to be supplemented by regular insulin as indicated by fractional urine specimens.

Other modified insulins have been suggested for the treatment of diabetes during the past two years. It has been demonstrated that certain basic amines, histones and other substances in combination with zinc will increase the effectiveness of insulin. There is no doubt that the chemical and physical properties of insulin determine its physiological action. In difficult cases neither unmodified nor protamine zinc insulin completely solve our problem. Perhaps after continued investigation and experimentation modified insulins may be developed to solve any diabetic problem. However, the so-called "tailor-made insulin" belongs to the future. For the present we are limited to regular and protamine zinc insulin.

Summary

At the end of two years, certain conclusions may be drawn as to the value of protamine zinc insulin. Its prolonged action makes available a constant supply of insulin throughout the day and night. Unfortunately, it is not a substitute for the normal pancreas as the insulin is liberated from its subcutaneous depot at a constant rate rather than in response to the physiological demands of the body. Protamine zinc insulin has undoubtedly facilitated the treatment of the mild and moderately severe diabetic previously controlled by thirty units or less of regular insulin. It has not solved the problem of the severe diabetic. Perhaps 25 per cent of these cases may be satisfactorily controlled with a single dose of protamine zinc insulin. Another 25 to 50 per cent may be controlled with

the aid of supplementary doses of unmodified insulin. In the remaining cases it has been possible to control the nocturnal glycosuria but it has not been possible to keep the urine sugar-free during the day without the precipitation of serious hypoglycemic reactions. Unfortunately, there are no criteria by which one can predict which cases will respond satisfactorily to protamine zinc insulin.

A distinction must be made between postprandial and nocturnal glycosuria in that the latter is derived from stored glycogen and endogenous protein. There is therefore reason to believe that the glycosuria after meals which is not associated with protein wastage or acetonuria is less harmful than that which occurs in the intervals between periods of activity of unmodified insulin. It is our opinion that this demonstrated ability of protamine zinc insulin to prevent protein wastage and ketonuria justifies its use in severe diabetics even if no more satisfactory control of the glycosuria can be attained than by repeated injections of soluble insulin. It would be unfortunate if this were interpreted to mean that control of glycosuria is no longer the essential aim of diabetic therapy.

There is no doubt that the use of protamine insulin requires greater care on the part of both the physician and the patient. The utmost care in the technique of administration and dietetic management which balances available insulin with available glucose will be necessary if satisfactory results are to be obtained. As other observers have pointed out, protamine zinc insulin has improved but has not simplified the treatment of diabetes.

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LIBRARY NOTES

RECENT ACQUISITIONS

A legacy, recently acquired by the Library from the estate of the late Dr. Lawrason Brown, fills a gap on our shelves with one of the truly great works in the history of medicine. It is unnecessary to dwell at length on a book so often described and praised, as "the first record of the use of immediate percussion of the chest in diagnosis," Leopold Auenbrugger's *Inventum novum ex percussione thoracis humani* . . . Vienna, 1761. It is with great satisfaction that we add this to our collection.

One of the most rare and interesting works which we have acquired in some years is an early English work translated from the French, the *Questyonary of cyrurgyens, with the Formulary of lytell Guydo in cyrurgie . . . with the fourth boke of the terapeutyke, or methode curatyfe of Claude Galyen* . . . London, 1541. It appeared in French in 1533 with the title, *Questionnaire des cirurgiens et barbiers avec le formulaire du petit Guydon* . . . The text relates that the *Questionnaire* follows that which the master surgeons and barbers of Montpellier used in testing those being examined in the art of surgery. Parts of it seem to be abstracts of excerpts from the great work on surgery of Guy de Chauliac. It is of particular interest as it demonstrates the little knowledge required by a surgeon in the years preceding the advent of Paré. With it is the *Formulary* of Guy de Chauliac, originally published in Latin with the title *Chirurgia parva* in the late fifteenth century. Nicaise maintains that it is very doubtful if this is the work of Guy de Chauliac, but some parts of it seem to be taken from his work. It is strange that although the text of Guy de Chauliac's surgery was translated into English not long after it was written (as our manuscript attests), yet it was not published in that language, so that the only printed English version to bear the name of that great surgeon is this little *Formulary*.

It may be of interest to quote from the preface to the volume written by Henry Copland, the translator: "Gentyll reders in consyderation that every scyence, arte, and faculte that are speculate & practysed by phylosophers, not onely ought to be shewed and taught unto suche as be present with them in theyr dayes, but also for a perpetuall benefyte to be set forth by wrytyngen vulgarily in every tongue, for the more eredines and erudycyon of all yonge and pregnaunt practycyens, as fayne wolde attayne to the perfycenes of every suche scyence, arte, and faculte. And not withstandynge that there be ryght many and sondry sortes, as well of very good and scyentyke bokes, as of ryght expert men within this realme in the scyentycall arte of cyrurgery. Nevertheles this lytell questyonary & formulary with the other bokes added therto have been often requyred and soughte for, to be had in englysshe (as well of me as of other) by dyvers and many persones of the sayde scyence . . . A certayne yonge gentyll man enured in the sayde scyence have a boke of the same in frenche moved the ryght honest persone Henry Dabbe bybliopolyst & stacyoner to have it translated in to englysshe. At whose instigacyon meanynge the help of God (though moste rudely) with the symplence of a good wyllyng herte I have enterprysed to do it in folowynge dyrectly my copy . . ."

In the history of medicine few figures are remembered for more outstanding achievements than the Italian physician, Marcello Malpighi, 1628-1694, whose fame rests on valuable contributions to anatomy, biology, histology, embryology and physiology. The Library has now acquired his work on another subject in two handsome folio volumes published by the Royal Society of London,

entitled *Anatome plantarum. Cui subjungitur appendix, iteratas & auctas ejusdem authoris De ovo incubato observationes continens . . .* London, 1675-1679, containing many full-page engraved plates. I can do no better than to quote from W. G. MacCallum's excellent article on Malpighi in the *Johns Hopkins Hosp. Bull.*, August, 1905.

"It would be impossible to enter into the details of Malpighi's enormous work which concerns especially phanerogams, but also some pteridophyta, fungi, galls, and parasitic plants. Hooke had seen plant cells and regarded them as merely cavities partitioned off from the general cavity. Malpighi, however, made a distinction between cells and fibers and vessels. With rare perspicacity he saw that all plants are composed of a complex of sacs or vesicles which constitute the fundamental tissues, and these he called otricoli. The generalization of this principle manifests the synthetic power of his mind. He had thus arrived at the modern distinction between parenchyma and prosenchyma, further than which he could scarcely go without a knowledge of protoplasm and the possibilities in the modification of cells.

His recognition of the continuity of leafstalks, branches, stem, and roots, and of the fact that the floral envelopes and cotyledons are modified leaves brought him very near to the ideas of Wolff and Goethe that all the diverse plant products may be traced from a few single types.

He described minutely with drawings of sections studied microscopically the wood and bark, the medullary rays, the tracheid vessels, scalariform and pitted vessels, sclerenchyma and woody fibers, the medulla, the nature of the annual rings, and so on, but erred in ascribing the origin of the wood fibers to the bast. From watching the growth of many plants he concluded that there was an essential difference between those which grew with one cotyledon only and those which started with two and thus divided as we now divide them, the phanerogamous plants. Not only this but he recognized that there is a fundamental difference in the arrangement of the fibrovascular bundles which corresponds with this division.

Most of his studies were, however, not merely morphological but sought to explain the physiology and laws of development of plants . . . Malpighi probably did not actually see the fertilization in the flower . . . Nevertheless, his work on the development of the ovum into the seed and of the ovary into the fruit and then of germination of the seed is classical.

He recognized the need of air for plants, and again with his zoophysiological ideas ascribed the function of carrying the air to the tracheids . . ."

Of his *De ovo incubato,* and his *De formatione pulli in ovo,* Garrison says that the plates accompanying it "make him the founder of descriptive or iconographic embryology, surpassing all other contemporary workers on the subject in the accurate notation of such minutiae as the aortic arches, the head-fold, the neural groove, the cerebral and optic vesicles . . ."

It may be of interest to note that in vol. I the letters are printed which passed between Malpighi and Oldenburg of the Royal Society in the years 1671 to 1675. See Birch's *History of the Royal Society,* vols. II and III for references to the correspondence which led to the publication of this work by that Society. The first mention appears on p. 499 of vol. II as follows: "Mr. Oldenburg produced and read a letter of Signor Malpighi, dated at Bologna Nov. 1, 1671, n.s. accompanying a manuscript containing an abstract of his observations and considerations of the structure of plants, which, he said, he intended to inlarge and to illustrate with figures, if he should find, that the society approved of his attempt . . ." On p. 179 of vol. III it is reported at the meeting of Jan. 21, 1675, that Mr. Oldenburg produced the manuscript of the work itself with a letter from Malpighi of August 20, 1674. On June 17, 1675, the Council met and ordered that it be published. The license was granted on June 24. The second volume, which appeared in 1679, was presented to the Society December 5, 1678, whereupon the Society ordered that it be printed.

G.L.A.

A SELECTED LIST OF PERIODICALS ADDED IN 1938

Journals which began in 1937 or 1938

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Chicago, Vol. 1, No. 1, Jan. 1938.

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Praha, Vol. 1, No. 1, 1938.

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Pittsburgh, No. 1, April 15, 1937.

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Saint Paul, Minn., Vol. 1, No. 1, Sept. 1938.

Archives des maladies professionnelles: hygiène et toxicologie industrielles.
Paris, Tome 1, No. 1, March/April 1938.

Archives de médecine sociale et d'hygiène et Revue de pathologie et de physiologie du travail.
Bruxelles, Année 1, No. 1, Jan. 1938.

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Leiden, 1925-29, [Vol. 1], 1938.

Bio-Morphosis; internationale Zeitschrift für Morphologie und Biologie des Menschen und der höheren Wirbeltiere.
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